Proceedings of the

TEACHERS' SEMINAR ON PHARMACOLOGY

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HELD UNDER THE AUSPICES OF THE AMERICAN
ASSOCIATION OF COLLEGES OF PHARMACY

AT

The University of Washington

Seattle

Edited by
JACK E. ORR

The Teachers' Seminars Are Made Possible By The Support Of
The American Foundation for Pharmaceutical Education

1957

FOREWORD

The formal papers and pertinent portions of the discussions of the Ninth Annual Teachers' Seminar on Pharmacology have been included in this Proceedings. The sessions were tape recorded in their entirety and manuscripts were submitted for editing to those authors who had not prepared formal manuscripts in advance. Human errors inevitably creep in and as a result the tape failed to capture most of the inspiring words of Dr. Chauncey Leake in his Sunday evening introductory address. It is regrettable that those who did not attend the Seminar are thus unable to share in the enjoyment of Dr. Leake's message which set the tone for the entire week, but the Seminarians are sure to remember it well.

The success of a Seminar such as this is necessarily a result of the efforts of many. On the local level this particular Seminar was a joint project of the College of Pharmacy and the Department of Pharmacology of the Division of Health Sciences of the University of Washington. Special credit should go to Dr. James M. Dille, Executive Officer, and Dr. Theodore C. West of the Department of Pharmacology, and to Dr. Nathan A. Hall of the College of Pharmacy. We are also indebted to the Department of Short Courses and Conferences for handling so efficiently the myriad of details associated with such an undertaking.

Development of a program is always a difficult task, a fact not properly appreciated until one has had the experience. The program for this Seminar differed from its predecessors mainly in the increased amount of time devoted to course content as opposed to teaching methods. The Committee felt that the subject of pharmacology, because of its particular nature, provided an unusual opportunity to experiment with the previously accepted format. It is our hope that the results of this "research" will be of value to future Seminar committees. The validity of the data must be determined by time and experience. Credit for the general excellence and high quality of the program must go to Dr. Ewart A. Swinyard, University of Utah, and to Doctors Dille and West.

The University of Washington was highly honored to have been selected as host for this Seminar, particularly so since it was the first such meeting to be held on the Pacific Coast. The registration of 113 from 42 American and Canadian schools of pharmacy, 10 medical schools, and 2 dental schools attests to the fact that distance, although creating a greater strain on already bent university travel budgets, is not necessarily a deterrent to attendance. We appreciate the dedication and interest which brought so many to the great Northwest.

To the members of the Seminar Faculty the Committee expresses its most sincere thanks for giving of their valuable time and talents to assure the success of the program.

As always we are most grateful to the American Foundation for Pharmaceutical Education for its generous financial support which makes possible the conducting of the Teachers' Seminar each summer. No other one thing has done more to improve the quality of pharmaceutical education in America.

Jack E. Orr
Chairman

TEACHERS' SEMINAR, 1957

Pictured above are teachers who attended the 1957 Seminar on Pharmacology at the University of Washington. Reading from left to·right are: (Row 1) J. E. Orr, W. C. Holland, A. L. Picchioni, Louis Fischer, R. W. Morris, E. Leong Way, Gertrude Falk, H. Keazling, E. Fingl, N. A. Hall. (Row 2) G. V. Rossi, E. J. Ireland, L. E. Fox, T. H. Meyers, A. C. Huitric, B. G. Fagg, T. D. Rowe, G. L. Webster, L. C. Zopf, J. E. Davis, T. C. West, B. A. Westfall, E. A. Swinyard. (Row 3) R. Voigt, Alta R. Gault, D. E. Green, F. T. Galysh, M. W. Jordin, L. J. Anderson, W. E. Johnson, R. W. Morrison, H. Bang, R. L. Russell. (Row 4, left side only) R. F. Gautieri, S. G. Mittelstaedt, D. Johnson, J. E. Halliday. (Row 5) R. S. McCutcheon, P. M. Scott, J. F. Bester, C. T. Ichniowski, D. E. Kroeger, R. K. Mulvey, P. V. Hammond, L. E. Gale, M. W. Green, W. C. McCarthy, N. M. Phatak. (Row 6, right side only) E. L. Platcow, H. K. Beecher, T. C. Daniels, D. C. Brodie, T. J. Haley. (Row 7) S. T. Coker, R. D. Gibson, N. W. Dunham, J. P. Buckley, R. M. Leonard, B. A. Barnes, J. A. Wood, W. M. Davis, L. W. Rising. (Row 8) R. J. Kahl, E. M. Plein, L. H. Saxe, D. G. Wenzel, M. J. Rodman, W. F. White, G. N. Aagaard, C. D. Leake, B. Rau.

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GREETINGS FROM THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

Tom D. Rowe

University of Michigan

By happenstance rather than intent, this seminar commemorates the 25th anniversary of the acceptance of pharmacology by the Colleges of Pharmacy. Many of you are probably not aware of this situation. Nor was I until I began preparing these remarks. This year also marks my 25th anniversary as a recipient of a B.S. degree in pharmacy. I remembered what pharmacology (so called) was in my school at that time and I thought it might be interesting to see what the over-all picture was a quarter of a century ago. Quite frankly, I was surprised to find it was such an important year for pharmacology.

In that year, 1932, the fourth edition of the Pharmaceutical Syllabus was published. This edition was to be the guide for the four-year course which became mandatory that same year. Pharmacology as a separate course was included in the Syllabus for the first time. Furthermore, it was a required subject. The outline for the course was reasonably complete, but the Syllabus Committee trod softly in presenting the material for laboratory work. The opening sentences in their description were: "The limitations likely to be found in the average school of pharmacy, particularly those which are not associated with a medical school, must be recognized in presenting this laboratory course. The laboratory work attempted must necessarily be simple and uninvolved." At least pharmacology had been officially launched but, apparently, with some concern as to the ability of the crew to handle the ship.

That same year the Conference of Teachers of Materia Medica changed its name to Conference of Teachers of Pharmacognosy and Pharmacology. This marked the first official recognition of Pharmacology by the American Association of Colleges of Pharmacy. The printed discussion of the previous year's meeting, which led up to the name change, makes interesting reading. From this material one gets the impression that pharmacology was still somewhat of a curiosity in pharmacy circles and not too well understood.

At the same 1932 meeting of the Conference, Marvin R. Thompson presented a paper in which he stated, "Only a few schools of pharmacy have courses in experimental pharmacology, but its possibilities merit discussion."

To paraphrase the song title "What A Difference 25 Years Make" certainly applies to pharmacology. Probably no other group in pharmaceutical education has made so much progress during this period. Today, as all of you well know, pharmacology is one of the most important of our professional courses and its importance is continuing to increase each year.

Even with this remarkable development, as late as 1951, a majority of our accredited pharmacy colleges did not have fully qualified pharmacology teachers. Dr. Deno, who had surveyed all of the 71 accreditei colleges, pointed out that

fact in a paper he presented at the first Teachers' Seminar on Pharmacology. He stated, "Unquestionably less than one-half of the colleges of pharmacy have the services of professional pharmacologists for the undergraduate courses."

I do not know definitely what the teaching personnel situation in pharmacology is today. Based on visitations I have made for the Council and on information gained from the study of some pharmacy catalogs, I would hazard a guess that the number of colleges not having professional pharmacologists today is less than twenty. Perhaps Dr. Green will have some definite information along these lines in his paper to be presented tomorrow. Thus, if my guess is reasonably accurate, we have reached a place in pharmacology where a large majority of the colleges have competent teachers for undergraduate work. I think we can expect all of the pharmacy colleges to be properly staffed by the time the next seminar is held in this field.

If your group is like the one I am most closely associated with which teaches the pharmacy subjects, and I am sure it is, you can attribute much of your recent progress to these seminars. While this is only the second one devoted exclusively to pharmacology, this subject was given considerable attention at the general seminar on pharmaceutical education. I'm sure your group benefitted as much from that meeting as did we in pharmacy. We had our second seminar two years ago and as a result of it, I think teaching of and planning for the pharmacy courses is at a higher level than ever before. I'm confident the same will be true for pharmacology as a result of this seminar.

The American Association of Colleges of Pharmacy is proud to sponsor these seminars. I think they are one of the most productive projects the Association has ever undertaken. We are indebted to the American Foundation for Pharmaceutical Education for providing the funds which make them possible. I know I speak for all of us in pharmacy when I extend our thanks to Dr. Briggs for the generous assistance the Foundation has given us for this project as well as many others in pharmaceutical education for which it has provided so well.

It is a pleasure to be in Seattle in this beautiful setting of the University of Washington. Although the meeting is just beginning, the program arranged assures us of a profitable and pleasant week. Obviously Dean Orr and his committee have worked hard in preparing for this occasion. My congratulations and thanks to them for a job well done.

Monday Session

INVENTORY AND PROSPECTUS

Ewart A. Swinyard

Chairman

THE STATUS AND NEEDS OF PHARMACOLOGY
IN THE PHARMACEUTICAL CURRICULUM

Melvin W. Green

American Council on Pharmaceutical Education

There was a time when the science of chemistry was emerging from the chrysalis of alchemy as a dynamic science. Laboratory space, equipment and proficient laboratory technicians were needed in numbers to bring about this metamorphosis. Where could these elements be found other than in the pharmacies of the old world? The times were right for pharmacy to come into its own in this atmosphere and, indeed, pharmacy became the mother of chemistry during this era in a very real sense. That portion of the history of chemistry cannot be written without interweaving with many threads borrowed from the history of pharmacy. To many this was the Golden Era of pharmacy. From this period on, the practice of pharmacy was closely associated with chemistry. The manufacture of many chemicals which served as drugs and the extraction of important alkaloids, glycosides, and other phytochemical drugs were closely associated with the art of the apothecary. Polypharmacy, which could equally well be called polymedicine, led to the necessity for understanding the chemical nature of incompatibility by the pharmacist, and small scale manufacturing in the pharmacy laid claim to a background in chemistry. It is but little wonder that the pharmacist has come to be clearly labeled as an applied chemist.

During much of this same period medical practice rested almost entirely on an empirical and authoritarian base. A perusal of the clinical literature indicates that use of drugs rested not upon true physiology, but rather upon observation that, regardless of how keen it might have been, was limited in its discrimination. Drug classification really had little significance beyond the descriptive, and the lore was aptly called materia medica.

The pharmacist's role during this period was important but clearly chemical in its orientation. He could be of little assistance to the physician on the pharmacodynamic side since the differences between two drugs said to be, let us say "alteratives," were associated with subtleties that existed very largely only in the mind of the physician and were more mystical than physiological.

The pharmacist's relationship to the public with respect to drugs, and nostrums sold over the counter at this time left much to be desired. In this the pharmacist was not to blame particularly. The items sold over the counter were often as much of a secret to the pharmacist as they were to the laity. Even if the pharmacist knew the nature of the contents of the package, he often knew too little of their physiological significance to perform much of an advisory function. Open labeling, potency of drugs in terms of central as well as side actions, and access to better biological background are all combining to make today's pharmacist a better adviser in these aspects of health.

Things could only begin to change after such scientists as Pasteur, Bernard, and Ehrlich came on the scene. The germ theory of disease, the experimental approach that could demonstrate a dynamic physiology and pathology at work during disease, and a chemical viewpoint that brought a basis for chemotherapy, all combined to lead to a more rational basis for medical practice, diagnosis, and treatment of disease. The way was now paved for the birth of the miracle drugs and the industrial revolution opened the path for their production in quantity. By now skilled scientists of many branches have developed their respective sciences to the point where a catalyst has been created permitting the rapid multiplication of all sorts of important drug developments. Since the manufacture of these drugs and even their dosage forms left the domain of the individual pharmacy for the industrial laboratory, the orientation of professional pharmacy is naturally away from chemistry toward pharmacology, and so the pharmacist is becoming less an applied chemist and more an applied pharmacologist.

No doubt it was this shifting responsibility of the pharmacist that prompted Dille to assay the position of materia medica and pharmacology in 1937. Those of you who remember the Dille survey recall that the status of pharmacology was low and the needs were many at that time. For the most part the field was then still designated as materia medica and clearly oriented in the direction of the name. Few schools were offering laboratory instructions in the area, very few truly professional pharmacology professors were in evidence and, often as not, pharmacology was only a part of physiology, pharmaceutical chemistry, pharmacognosy or some other subject. A factor of equal importance in impeding pharmacological progress was the paucity of biological support for a modern program. Out of 55 schools of pharmacy, Dille showed that only 22 had a year's course in biology or the botany-zoology equivalent and only 39 colleges offered physiology.

By the time of the first pharmacology teachers' seminar, held at Purdue in 1951, the situation had obviously improved. Deno's analysis at that time showed that 53 out of 71 schools offered a year of biology and 15 schools offered either botany or zoology alone. My own analysis for 1956-57 showed a somewhat improved picture and certainly a shift away from botany toward biology and zoology. The current survey shows, also, an improvement in the anatomical basis for physiology in that nearly three times as many schools now require a semester of anatomy alone and about four times as many schools now have a year's course in physiology which is presumed to have considerable anatomic content. Presently, only seven schools have no physiology and two no microbiology as such. Fifty-two of the colleges require biochemistry, but most of the remaining accredited colleges cover much of the content of biochemistry in other courses. This information is summarized in Table I which shows that some progress has been made in providing a better biological background for a stronger pharmacology program. A study of the seven schools that had a five-year or six-year program only in operation last year shows that four of them required anatomy and the other three had a year's course in physiology.

While decided increase in the amount of biological science taken by pharmacy students in preparation for pharmacology took place between 1937 and 1951, it is my impression that many pharmacology teachers believe that there is considerable room for improvement yet. If the beginning biology courses are the rather typical grasshopper-type surveys, and if the physiology is weakened by lack of anatomy and appreciation of the relative importance of muscle physiology and autonomic

physiology, the student may be ill prepared for pharmacology. In discussing pharmacy students with teachers of pharmacology responsible for the instruction of both pharmacy students and medical students, I am usually told that the pharmacy student has the advantage of a superior knowledge of the chemistry of drugs and related actions; a vocabulary about drugs, and a high morale coming from his knowledge that pharmacology is, to him, one of the important capstone courses. On the negative side, I am usually told that the pharmacy student is deficient in knowledge of basic anatomy and histology, the implications of embryology and certain basic tenets of physiology especially neuro-physiology. Pharmacology teachers often struggle against these deficiencies by reviewing and augmenting fundamental biological training.

So much for the status of the preparation for pharmacology, what about pharmacology itself?

The basic course in pharmacology, now largely called pharmacology, is a year's course (although frequently laboratory work is given only for one semester), and varies somewhat in the total number of clock hours given. In nearly every case it is a senior subject, although occasionally it is distributed between the last half of the junior and the first part of the senior years. Table II showing the clock hours of instruction given in the first course shows little deviation from the Deno survey of 1951. Since both Deno and I had to make certain assumptions relative to the number of weeks in the school year, etc., the differences between us may actually only be due to these factors rather than changes in the instruction pattern.

At the time of the Deno survey there were five schools that gave didactic instruction alone in pharmacology and while the present catalogs show the same number, at least three of these situations are corrected or in the process of being corrected. From these data it would appear that a standard pharmacology course is essentially three hours of didactic instruction per week for a year and one three-hour laboratory either for one or two semesters.

An important factor governing the instruction in pharmacology is whether it is taught by professional pharmacologists or not. In general, professional is defined in terms of graduate education in the field of specialization at the doctorate level, membership in professional societies, and publication of the results of research in the field. It frequently follows that a given person does not meet all of these criteria; he may be new enough at the game to have few or no publications, he may not have been sufficiently experienced in research to meet the membership requirements for his professional society or, because of some other circumstance, judgment may have to be used in classifying him as a professional or not. In all cases where the pharmacology instruction was given in the medical school, it was considered to be in the hands of a professional. Actually this is open to question since many such pharmacologists are displaced physiologists, biochemists and other medical scientists.

At the time of the Dille survey it is evident that there were comparatively few professional pharmacologists in the picture outside of the medical schools and the professionals appear to have been viewed with some suspicion. In the judgment of Deno in 1951, there were then 20 pharmacy schools having at least

one professional pharmacologist, and 14 others having access to medical school pharmacology. At present there would appear to be about 45 pharmacy schools with instruction in the hands of one or more professionals, and 12 others where the instruction is in the medical schools. This is a decided improvement, for Deno stated in 1951 "if my impressions are well-founded, then more than one-half of the colleges need a professional pharmacologist." It would appear on the surface that a minimum of 18 would be needed today. However, in some of the schools where the instruction is not in the hands of a professional, by definition, the instruction is good, modern, and vital.

A significant measure of the status of a field is graduate work, and research, also. This is a phase of the profession not easy to assess in objective and qualitative terms. There are at present 22 schools offering work limited to the master's level in pharmacology and 25 offering the doctorate. Twelve of this latter group offer the work only in the medical school. In several instances there is excellent cooperation and collaboration between so-called medical pharmacology and pharmaceutical pharmacology at the graduate level.

Last year there were 321 papers published by 143 pharmacy school staff members. I do not know precisely how many of these are pharmacology papers, but I would think it would be more than a fourth. As one visits colleges of pharmacy it is impressive to see how many pharmacologists have research grants from the University's research foundation, the U.S. Public Health Service, the Armed Forces, industry, and other sources. In other words, pharmacology is clearly coming into its own as a scholarly and research-minded profession in the school of pharmacy.

The needs of pharmacology are something that you seminarians know better than I. It would seem to me that the needs revolve around staff, curriculum, and facilities. In these respects the needs of pharmacology are parallel to the needs of other departments in our colleges.

With respect to staff there certainly should be a minimum of one professional pharmacologist per college of pharmacy, discounting, of course, the special situation where pharmacology is taught in the medical school. Many schools with a strong research interest need additional staff in this department in order to divide teaching load, to enable more research to be done, and because the staff is doing some teaching of nurses. Of almost equal importance is the need for technician assistance, mechanics, and the like. It is difficult to find a pharmacologist who is not at least distantly related to Rube Goldberg. He needs additional mechanics' hands to enable him to give freer reign to his gadgeteering. The pharmacology teacher usually needs better access to stenographic and clerical personnel also. Much material that I hear being dictated in class should be available as "handouts" so as to conserve class time.

At present, facilities for pharmacology run the spectrum from the barest essentials to the most elaborate. There is no school which could not use additional facilities and equipment. When you ask an instructor what he would like to have in the way of equipment, it is interesting to observe that almost invariably it is the teachers who have the best equipped laboratories who can give an almost immediate list of needs. "To him that hath shall be given" is no idle phrase. Demonstration and teaching programs should not be determined by the equipment available but by the educational dictates of an alert staff.

Pharmacology teaching lends itself to the use of models, demonstrations, movies, television, and other audio-visual materials. The needs for these apparatus should not be overlooked. It is an important need, also, to make the best use of such facilities. Possibly one of the valuable features of this Seminar will be discussions of the use of audio-visual methods.

In matters of curriculum, it has been indicated before that in many schools a better biological background for pharmacology appears to be desirable. Pharmacology is, by definition, an applied science not a basic one. If, however, the student is ill prepared in the basic sciences, he cannot make the application with full-meaning. The result is that the pharmacologist must take the time to teach basic science material or give the student only an imperfect knowledge of the phenomenon with which he is dealing.

This leads to a related matter that is difficult to handle--the preparation of the student in the terminology of applied therapeutics. Therapeutic literature is full of reference to disease names and characteristics that the medical student becomes familiar with in courses in internal medicine and the various specialties in a systematic and meaningful manner. I am thinking of terms like petit mal, pulmonary embolism, vascular encephalopathy, the Schwartzman phenomenon, myasthenia gravis, myocardial infarction, Parkinson's disease, cardiac decompensation, milliary tuberculosis, thromboembolic syndromes, thyroid neoplasia, fulminating hepatitis, Boeck's sarcoid and the like. The list could be expanded if consideration were given to medical slang. To be maximally helpful, the pharmacist should be at home in the physician's terminology at least as it may affect drugs. Aside from the terminology that springs from the basic medical sciences, the only approach appears to be merely one of vocabulary building at the moment. This is so important that, if it is the only way of accomplishing the objective, it certainly should be done. One or two colleges have courses in medical orientation which may supply at least part of the answer.

We now come to the time allotted for pharmacology itself. Nearly every pharmacologist will claim that he wishes he had more time. For that matter so will the specialist in each of the other four pharmaceutical disciplines. More time is asked for on the grounds that (1) the pharmacist must be familiar with all drugs not just those of primary importance, and there are more drugs today than ever before, and (2) the pharmacist must know more about related subjects like toxicology and bioassay than can be crowded into the basic course. Those who do not believe more time is necessary point out that the basic principles can be taught within a reasonable length of time and that it is not necessary to have encyclopedic knowledge of each and every drug, but that the student can be taught to apply principles as he reads about drugs in the literature. This group will point out, also, that by choosing laboratory experiments with discrimination, laboratory time can be conserved without loss of principles. This issue is one which will be discussed undoubtedly during this seminar. Certainly it is one for pharmacologists to decide and not for an outsider such as myself. The issue represents a philosophy of education that presents problems to all phases of pharmaceutical education not only pharmacology. All of us need to look at our fields of learning carefully and thoughtfully to distinguish between that which is well to know and that which is necessary to know. One must be aware always, that we are trying to make the pharmacist a genuine authority on drugs in a professional and not in a scientific sense.

Lastly pharmacology, no less than other sciences, needs to develop strong research programs. If the field is going to have the respect it deserves it must be centered in research of the highest significance and not in trivia. Much of the pharmacology research we are discussing is centered in pharmacy schools. Such research can and perhaps should be pharmaceutically oriented. I am sure that good sound basic research can be so oriented. This is an orientation around the dosage form to a certain extent. I have reason to believe that we have accepted the value of many dosage forms on pharmacologic or perhaps even pharmaceutic faith with little experimental evidence. I am thinking of the importance, pharmaceutically, of the studies by Dille and Hazelton on the retarding action of glycerin on the absorption of certain drugs, notably phenobarbital. I am aware of the studies of Campbell and his Canadian associates which cast considerable concern about the availability of some drugs and vitamins in certain compressed tablet preparations. These and other pharmaceutic problems are applied problems but they can be approached in a basic and broad manner. Those of you who have become familiar with the survey on Medical Research published under the aegis of the American Foundation are aware that the measure of medical research, which like pharmaceutical research is applied, is the degree of its fundamentalness and the breadth of its scope. Pharmacology is a biological science and it draws upon other biological sciences, therefore, and it draws as well upon physics, chemistry, and mathematics if it is really as thorough as it should be. It is essential that research done in pharmacy schools be qualitatively of a caliber equivalent to that done in medical schools if it is to have the respect that it should.

While the strongest research centers will be undoubtedly in the graduate centers, all colleges of pharmacy should be conducting some research. One of the trademarks of a professional school is research activity--without it how can there be professional growth?

Lastly a need in pharmacology is the assurance of a continued flow of able young men and women into graduate education to become professional pharmacologists particularly for pharmaceutical teaching. There is a normal attrition in the field due to death, retirement, and entrance into related teaching positions and industrial research which increases the need created by departmental expansion. Further, if the field is to gain increased status at least some of the new pharmacologists must go farther as teachers and scholars than their teachers. Moses, said by many to have been the world's first great teacher, having led his people from the wilderness and its trials and tribulations, came at last to a high point where he looked upon the Promised Land which he could never enter but which his followers would possess. There must be a Land of Promise for youth better than that possessed by its elders, else how could the next generation advance?

TABLE I

Number of Schools Offering
Pharmacology Prerequisites

	1956-57	Deno (1951)	Dille (1937)
1 year Biology or Botany-Zoology	58	53	22
Botany alone	9	12	-
Zoology alone	7	3	-
Anatomy required	21	8	-
Anatomy and Physiology, 1 year	19	5	-
Physiology	48 (67)*	44 (49)*	39
Microbiology	72	67	-
Total number of schools	74	71	55

*Total number schools requiring Physiology

TABLE II

Clock Hours Instruction in Pharmacology

	Mean		Median		Mode		Range	
	Now	Deno	Now	Deno	Now	Deno	Now	Deno
Lecture	94	98	90	96	90 (25)	96 (19)	30-192	33-192
Laboratory	68	71	60	64	90 (27)	96 (23)	0-180	0-192
Total	162	169	160	160	180 (20)	192 (17)	90-270	64-288

THE USE OF PHARMACOLOGY IN RETAIL PHARMACY

Jerome C. Kopet

North Hill Drug Store

Spokane, Washington

The use of pharmacology in retail pharmacy concerns principally the practicing pharmacists in a retail establishment, that is, those employed in a professional pharmacy, where 50 per cent or more of sales volume is derived from prescriptions; or in a large neighborhood store like mine, where over 25 per cent but less than 50 per cent of my volume comes from prescription services; or in a super-market, which in this part of the country does have a prescription department but which contributes insignificantly to the sales volume; or in a "corner" drugstore where a prescription interrupts the normal routine of the sole proprietor. To some extent, a hospital pharmacy may be considered as a retail outlet, but since that category is to be considered immediately following this presentation, and since it appears to be an entirely different approach, I have not considered it in my remarks.

In January 1956 the National Association of Boards of Pharmacy reports that roughly 87 per cent of the registered pharmacists were engaged in the retail field and an additional 3 per cent were engaged as hospital pharmacists. David Kendrick of the University of California published in California Pharmacy for April 1957 the results of a survey of the employment status of the active registered pharmacists in California as of May 1956. His figures are substantially the same as those of the N.A.B.P. Nine out of ten of the undergraduate students of pharmacy schools will end up in retail categories. One student out of ten who completes his registration or graduates will find himself in one of the associated practices.

Now what opportunities do these nine out of ten registered pharmacists have to put their knowledge of pharmacology to use? I believe, from my experience, that I can list the following duties or obligations as those which concern the practicing retail pharmacist or which are often mentioned as being important, and which are also closely concerned with the "science of drugs, including materia medica and therapeutics." This list includes: 1. The filling of prescriptions. 2. The detailing of physicians. 3. The serving as a liaison between the physician and the public, which may include explanations to the public in general terms. 4. The advising of customers concerning new pharmaceutical products which are often enthusiastically promoted by the not too ethical lay press.

I had the opportunity of discussing the "Use of Pharmacology in Retail Pharmacy" with a number of men so engaged, and my most pertinent comment is that you gentlemen may be excellent instructors, skilled researchers, and able administrators, but you are not very good salesmen. You have failed to impress your students with the importance of pharmacology to the practice of their profession. They overlook or do not realize how basic the knowledge of pharmacology is in their pharmaceutical education. It is the one subject the knowledge of which sets them above a vocational school-type trainee.

It is possible, and I know from actual experience, to take an intelligent high school graduate who can type, and train her to do accurately 100 per cent of what a registered pharmacist does 95 per cent of the time. She can take prescriptions from a physician over the phone, and as a State Board member I could find no provision in Washington Law that this is not legal. She can read prescriptions accurately. She learns dosage forms and dosage units of proprietary products. In 95 cases out of 100, she can count out or measure out a single item, make a correct label and put it in the proper container. Why not send her to a vocational training school for six months so she can learn a little bit about weights and then she can mix ointments and stomach powders, too? At the present time, if you can't buy an ointment at wholesale already prepared, you probably are only diluting one that is furnished by a manufacturer and it's easier to combine than making a cake frosting anyway.

She gets along just fine until something arises that requires the exercise of judgment. She would find nothing wrong with a prescription for digitoxin 0.2 mg., No. 100, Signature: 1 tablet three times a day. A pharmacist wouldn't fill it without a satisfactory explanation from the physician that he meant to write one tablet three times a day for three days, and then one daily. It is pharmacology that opens up areas for the exercise of judgment for a pharmacist.

It is difficult to judge the importance of each of the courses that are given in a pharmacy school when surveying the finished product, but it is my studied belief that pharmacology is the most important subject that a pharmacy student must master. He would be only a skilled technician if he did not have the basic knowledge required, and the specific knowledge obtained in the study of pharmacology. It doesn't take much knowledge to fill a prescription for present-day medication, but it takes a firm knowledge of the subject to check it out to the patient.

I have not found that the detailing of physicians requires any great knowledge of pharmacology, principally because we don't do very much of it in our city. The important pharmaceutical houses take care of that for us, and judging from the amount of time that pharmaceutical salesmen are out of the city, they must take care of it in the small towns also. The last few questions that I have had from the active physicians consisted of these:

> "Is there any contra-indication to use of this oral treatment for trichomonas if the patient is pregnant?" I looked the answer up in the drug encyclopedia while he waited.
>
> "What's the name of the new product that combines an antihistamine and an analeptic?" The physician used the trade name of each and I had been detailed just as the physician had. I happened to remember the name.
>
> "What is a real good hematinic that comes in a small capsule?" I suggested one that we buy in thousand quantities.
>
> "Will you fix for this 65-pound boy a round of the piperazine anthelmentic and give his parents an instruction sheet? I can't find my dosage chart." I use the same booklet the doctor has in his office and furnish two ounces with the instructions of one teaspoonful twice a day for seven days.

"What is '________'," and the physician mentions a proprietary. I get the bottle from the shelf and start to tell him that it is the diethanolamine salt of p-tolu- etc. I am stopped and asked what it is used for. While the physician waits, I look in the manufacturer's catalog and find the word cholagogue. That is all the man wanted to know.

I don't need to ask for an appointment to detail the physician as it would be a duplication and a waste of his time. I accomplish the most by informally discussing what size outboard motor the good man should get for his new boat.

I agree that my pharmacists could do a good job explaining drug actions to the physician, but it just isn't needed. I detail my store, my services, my reliability, my desire to serve him and his patients, and I use very little pharmacology in this chore.

In the last five years there has been a tremendous change in the attitude of the average individual towards the value, importance and potency of the medicine that the physician has prescribed for him. A prescription is no longer a more convenient, though more expensive, way of obtaining a medication that Grandma could prepare better from her old formula out of the medical book if she had the time. The results of the research of the pharmacologist has produced more potent and more specific medicaments. The contra-indications and side-effects of the medications used today are matters of much greater import than they were with the products generally used ten to fifteen years ago. I also place a great deal of credit for this increased respect of the importance of proper medication for proper periods upon the Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act. I will agree that this amendment placed restrictions upon the actions and the exercising of the judgment of the dispensing pharmacist. However, I never did feel that I could judge whether this man needed to continue to take thyroid, or whether this customer was taking more phenobarbital than he should, or that this woman was fat enough to require dextro-amphetamine continually. Whatever the other values or detriments of the law may be, it certainly did standardize our refilling procedure.

Prior to April 1952, in this part of the nation, very little attention was paid to the prescription-only legend. Prescriptions were generally refilled indiscriminately. Some attempt was made by some of us to limit quantities of potent substances used, but generally money in the till was what was the most important. If we attempted to call the matter of mis-use to the attention of the prescribing physician, we were often rebuffed and told that compounding was our business. If we attempted to call the matter of mis-use to the attention of the patient, he often became indignant, asked for a copy, and got his prescription filled someplace else. There was quite a revolution at the very first when we were unable to legally furnish medicine to a patient who had been using it for years without our first checking with his doctor. It took a lot of tact, and time, and patience to satisfy the customer that we were not acting in collusion with the medical profession to the detriment of the individual. It took expert knowledge of the pharmacology of the medication in question to convince him that it was only in the interest of his welfare that such caution was required. It took tact and a simple everyday vocabulary to convey the importance of the

precautions in each particular case without frightening the person being treated, or without giving false information, or without betraying the confidence or purpose of the physician, particularly for those medical practitioners who have the desire or the cause not to inform the patient of exactly what he is being treated for.

Those of the dispensing pharmacists who took the time to explain carefully in each separate case have been amply rewarded. We have no trouble now. People seem content to allow us to follow the legal procedure for refills. We are not afraid nor ashamed to tell them, "Your doctor says that he wants you in for a check-up before you take any more of your asthma medicine." And the customer is not irritated upon being told he has to make an office call. It was not easy at first to obtain the cooperation of members of the medical profession either. They resented the bother and the time that was required. But I remember so many cases when we called for the first time for permission to refill legally a prescription that we had been filling for a long time, the doctor would say that he hadn't seen the patient for years. Gradually they began to realize that there was value in what we were required to do, and now we enjoy wonderful cooperation. The physicians appreciate our efforts in the interests of good medicine.

The point that I want to make is that those of us, who tried to treat the situation with the proper attitude and not just abruptly blame some conniving congressmen in the national capital as some of our colleagues did, have performed a service to our profession. The work we do and the material we supply is held in much higher regard now than a few years ago. We were able to accomplish this not because of our knowledge of compounding, nor of chemistry, nor of pharmacognosy, nor of arithmetic, but because our knowledge of pharmacology gave us the facts and the judgment to do the right kind of a job.

I don't know whether you are aware of the fact that a great number of the people of this country are very suspicious of any kind of prescribed medication. You gentlemen are so cognizant of the theories of drug action that you have no questions as to the value of medical or chemical therapy, and so it is with the medical profession; but not always is it so with the laity. I think you will also find it true that a great number of our people are somewhat suspicious of the medical profession.

The retail pharmacist is the last station in a long train of specialists. He has more contacts with the consumer than any of the others who are concerned with furnishing a good and proper medicament for an illness. The retail pharmacist is asked many times such questions as, "Does this Doctor know what he is doing?" or "What medicine did he give me?" or "Why did he change my medicine?" or "What is this medicine for?". These questions present a difficult situation. The correct "Mayo nurse" answer of "Ask your Doctor" doesn't seem to suffice in present-day pharmacy. Here is where you have to be very discreet and as one pharmacist put it--"somewhat coy." A valid answer and an honest answer is required. It must be an answer that does not frighten your patient but reassures him. It must be an answer that his physician would not object to. His physician either talks in terms that are not included in the patient's vocabulary, or hasn't taken the time to explain, or else the patient is afraid to ask him. It is often a matter of translating what the doctor has said into terms that an

automobile mechanic can understand. You have to take the term antipruritic and make "stops itching" out of it, or the term anticholinergic and make "stops your bellyache" out of it.

It is not the knowledge of galenicals, nor of quantitative analysis, nor of organic chemistry that you call upon to handle this situation. It is the knowledge of pharmacology that furnishes the proper answer many times each day.

The public becomes aware of new treatments generally in two ways: extensive advertising in the case of proprietaries, and newspaper stories or magazine articles in the case of medical advances which will assist a prescribing physician. Now not all proprietaries are completely worthless, although they may be greatly over-priced. Some of the combinations do have real merit but the claims for them may be greatly exaggerated. It requires a thorough knowledge of pharmacology to be able to say that this product is a good analgesic, that the rationale for the use of citrus bioflavinoids in certain combinations for self-medication is sound reasoning, that this expectorant is better than that one. I will grant that you people may have good reason to object to this type of commerce, but believe me, it is big business today. In most cases the customer has been pre-sold by radio or television or the evening paper by the time he appears at my counter. How can I keep faith with these people unless I know what I am talking about when it comes to the pharmacological aspects? It is pretty well accepted today that it is advisable to supplement our modern day diet with a vitamin combination and it is common for the physician to tell his patient to ask his pharmacist to pick out a good combination for the person to take. I have heard of some very effective door-to-door salesmen and I have employed some very good nonregistered drug clerks, but the person who accomplishes the most for both the patient, the doctor, and for me is the pharmacist who is well versed in pharmacology.

It often happens these days that the laity has an intimate knowledge of a new and potent therapeutic agent before the clinical trial has been completed or before the value of this substance has been accepted by the medical profession. You would be surprised how many times a clipping from a magazine article is presented to a pharmacist and the questions asked, "Is this product any good?" or "Why can't I buy some," or perhaps, "Why isn't my doctor using this?". It is interesting to note that the present marketing company for the new oral product used in the treatment of diabetes has taken great pains to outline the potentialities and limitations of this preparation to the pharmacist and has asked him to tell the story to the insulin user. It is pretty obvious as to what part of our pharmacy education will assist us in furnishing the answers. The laboratory courses and techniques not only underline the knowledge that must be retained but also bring forth a familiarity with certain styles of medical equipment that are used in home treatment and for which the pharmacist must furnish the instructions.

In conclusion let me reiterate that the subject of pharmacology is the most important and will be the most commonly used portion of the professional education for nine out of ten of the pharmacy students who attend upon your lectures, or labor long hours in your laboratory courses.

As I look over your program for the next few days I feel an old thrill coming back. How fortunate are you teachers who have the experimental aspects of this subject to use as a recreation, or a hobby, or a refreshment of strength and spirits after toil. But do not fail to see to it that your student has an understanding of the words used, of the principles involved in pharmacology, and the ability to use them fluently and effectively. He has to be sharp and to keep up with his profession.

And to you gentlemen may I say, "Sharpen up your salesmanship." Very few people, even those otherwise well-educated, know what a pharmacologist is or what he does. It often takes some discussion even among your recent graduates before they will agree that pharmacology is really important to them. They just hadn't thought of it before. The State of Washington doesn't even include pharmacology in its required examinations for registration. Call it public relations if you will, but sell what you are doing. You are young, but you are growing rapidly.

THE HOSPITAL PHARMACIST'S USE OF PHARMACOLOGY

Louis C. Zopf

State University of Iowa

Through your own testimony you admit the complexity of subject matter defined as pharmacology. You agree that pharmacology especially embraces the area of drug therapy. In fact, one of the pharmacology texts is entitled, The Pharmacological Basis of Therapeutics. It seems unnecessary and presumptive on my part to go into further detail regarding the definition of pharmacology. This we will assume is thoroughly understood. Speaking in the capacity of a pharmacist, I shall discuss the use of pharmacology in the hospital pharmacy as it pertains to therapy and as it serves in the capacity for the improvement of the rational clinical use of pharmaceuticals.

The general principles of pharmacological consideration of therapeutics include mechanism of drug action, cellular response, relationship to clinical structure, drug absorption, distribution, and ultimate fate and excretion of the drugs. These are generalizations, accepted by you as pharmacologists, and with which other allied professional groups generally agree. Much has been written and additional information will be disseminated at this Seminar which will modify, expand, and, we hope, clarify the problems of pharmacology as a science.

Bachmeyer and Hartman in their text, The Hospital in Modern Society, make the following statement: "Fundamentally, hospitals are one type of institution created by society for service to society. Their existence implies a need for the service and their future growth depends upon the degree of usefulness that can be developed. Beyond and above a hospital's service to the sick individuals in its beds, to the medical profession, to the cause of medical education, and to the growth of human knowledge, stands that hospital's final resultant in real service to society as the ultimate measure of excellence." These administrative experts also say that, "there is yet occasionally a hospital performing only the first elementary function of a hospital--the furnishing of bed and board to a sick individual; but there are now many at the other end of the scale giving service which is the product of hands skilled in many ways and the work of several professions..."

The improved physical facilities of hospitals as hostelries for the sick, while representing a major transition in medical care, is not our chief concern. Important as this may be, we are primarily concerned with the effect which scientific progress has made in the change of professional services to the patient. We are prone to forget the evolution which is taking place through scientific efforts in the development of improved drug therapy. Organic chemistry, an infant thirty years ago, has since that time developed into a Herculean giant, and demonstrates a maturity whcih tends to exceed our ability to comprehend. Physical and biological chemistry are expanding our basis of understanding the mechanism of biological reactions. Through these expanding sciences, we have

available a type of information which must be understood by the professional personnel whose responsibility it is to provide therapy for the sick. Chemobiodynamics and the use of radio-isotopes are now common instruments for determining clinical responses, and are most useful to delineate the site of action or disposition of certain pharmaceutical substances introduced into the human body.

Pharmaceutical product development has received a much needed stimulus through the availability of the expansion of scientific information. Improvement in dosage forms has been greatly facilitated through the multiplicity of new materials, which have or may possess a potentiating factor of improved drug mechanism. New processes of exacting methods for drug isolation and drug compounding have had a revitalizing, innovating impetus on pharmaceutical product design. The expansion of our "knowhow" of the new chemical compounds and especially our ability to depend upon methods of pharmacological studies, has revolutionized the old adage that substances cannot be used therapeutically because of their toxicity.

A leading pharmacology textbook lists pharmaceutical preparations of crude drugs, but gives little mention, if any, to the more popular dosage forms--the tablet, the suppository, the aerosol. It gives but passing notice to a highly accepted form of medication--namely, injections. This same author discusses some of the more toxic and highly potential substances, such as the hormones, radioactive isotopes, nitrogen-mustards, and antibiotics. And yet, nowhere in the text is there a statement of caution regarding the effect which may be expected from the use of newer solvents, surfactants, emulsifiers, or diluents. Certainly, this is a pharmaceutical problem. I wish to direct your attention to the hospital pharmacist's need for knowing the pharmacology of the active medicinal agent and the necessity of understanding the effect which additive substances may have on the mechanism of the active component in the human cell. Clearly stated, the hospital pharmacist is interested in therapeutics. He must have a thorough understanding of pharmacology because he will be associated with a variable professional group. The clinicians are more concerned with the physiological responses of the drug than in their molecular configuration or pharmaceutical design. There are very few persons associated with the average hospital who are either interested or qualified to do good pharmacological research. The size of the pharmacology textbooks is recognition of the tremendous basic information available, classified as physiological responses. It should not be difficult, then, for us to envision the necessity of having the hospital pharmacist well-qualified in the field of pharmacology--call it therapeutic or practical pharmacology, as you please.

During the past two years, approximately eight hundred new drug products have appeared on the market. To classify these new drug products requires a basic understanding of chemistry, pharmacology, and pharmaceutical product design. The physicians and other professional personnel do not have the time to review the products themselves, and even less time to consider their pharmacology. The pharmacist must serve as a drug consultant. His understanding of pharmacology must be adequate to serve him with confidence if it becomes necessary to catalog a drug as to its proper classification. He must understand the mechanism of systemic response and have complete knowledge of the possible results through combinations of drugs. In brief, he must understand the pharmaceutical chemistry, the method of administration and the drug's therapeutic potential.

In the average hospital, the pharmacist is the only other individual of professional status who is on a par with the physician in his understanding of pharmacology. It is not uncommon for five to twelve detail men to visit a hospital on one day and for each of these to present a drug which fundamentally, pharmacologically speaking, is a mere modification of product design for sales potential rather than product design for therapeutic manifestations. Someone in the hospital must screen drug products. This should originate and perhaps terminate in the pharmacy, through the combined cooperation of the therapeutics committee.

The pharmacist usually serves as the chairman or secretary of the Therapeutics Committee of the hospital. In this capacity he must be competent to discuss therapeutics with the clinicians. Although the Pure Food and Drug Laws today have erected barriers of caution and protection for patient safety, there are still many new drugs which find their early clinical dosage solely dependent upon the study which they receive in various hospitals in our country. It is not unusual for the pharmaceutical companies to make their product available in the early exploratory phase with meager information relative to possible adverse reactions and problems of solubility and compatability with other therapeutic agents. The pharmacist must, therefore, understand the physiological action of a drug if he is to assist the physician in his effort to obtain a higher degree of biological response in the patient.

As mentioned previously, the availability of many new chemical substances has greatly enhanced the pharmacist's opportunity to establish improved pharmaceutical products. Even 15 years ago we gave little consideration to the increased activity of a drug when applied in a media where the surface tension of the vehicular agent was so changed that the active constituent became more intimately associated with the tissue. Little consideration was given to the change in physiological response due to the addition of the solubilizing or neutralizing components. As an illustration, the effects of changes in pH were long disregarded in therapeutic considerations and their actual effect had to be demonstrated _in vivo_ before we became concerned. How can any hospital pharmacist pretend to perform the functions of his duties if he does not understand the pharmacological responses of an agent which has been potentiated because of certain additive compounds?

To assist in a program of rational drug therapy, it is desirable that the pharmacist know where the drug is to act. Must it reach the lymphatics? does it get into the blood stream? if it acts locally, how does it act?--the mechanism of that drug is important. If it is desired that there be a greater dispersion of this material, then the pharmacist must understand how to achieve this effect, or shall we say, even how to control it.

There is a multiplicity of ways in which pharmacology enters every transaction emanating from the hospital pharmacy. True, the pharmacist does not, and should not, and has no reason to diagnose or prescribe; but he must know the resultant therapeutic effect of every drug which he dispenses. It is his obligation to be fully aware of the toxicology involved and to alert the physician concerning any adverse reactions which might be attained through use of a drug in combination or as a single unit.

To summarize, the hospital pharmacist uses his pharmacology as a guide to rationalized methods of drug therapy, and in certain hospitals the pharmacist is requested to teach pharmacology to the nurses. He must be in a position to understand the clinician's terminology and to assist the interns and residents in the understanding of new drug products. His is the obligation of knowing the resultant therapeutic effect from drug combinations and from variants in dosage forms. He must know the effect of solvents, surfactants and other agents on new medicinal products. If these substances complex, do they enhance the absorption potential or do they inhibit the physiological responses? These are the needs for a thorough course in pharmacology for the hospital pharmacist.

THE USE OF PHARMACOLOGY IN INDUSTRY

Victor A. Drill

G. D. Searle & Co.

Here we bring up a new phase of pharmacology as we talk about pharmacology in industry, an area of work that is quite new. We heard last night from Dr. Leake how various aspects of pharmacology have developed slowly over a period of many years and how only in about the early 1930's pharmacy schools had recognized pharmacology as a subject that should be taught regularly to the students. If we look back in industry there was actually little use of pharmacology as we now know it, in the industrial laboratory. There were some men in industry in the early 1900's, but relatively few people went into that work. The field itself was somewhat in disrepute and it was thought, in a sense, a little dishonorable for a man to go from academic work to an industrial laboratory.

Things began to change in the early 1920's; a few more people went into the field, but pharmacology in industry as we know it today really didn't begin until the latter part of the 1920's or early 1930's. Dr. K. K. Chen, Past President of the Pharmacology Society, was one of the first persons to really get into this area and develop industrial pharmacology. In his presidential address a few years ago he reviewed some of the troubles that he had in this area, including the fact that the Pharmacology Society did not recognize people who worked in such an area. All that has changed, pharmacology in industry is now quite well recognized and the area as a whole has made great strides in the last 25 years.

Part of the delay in the association of pharmacology with industry depended on a number of things. Pharmacology, as you know, is a science that depends on other sciences. We have to know physiology quite well, we have to know biochemistry, and until sciences of that nature were developed and thoroughly understood, pharmacology itself could really not develop. Pharmacology is the best link we have between these other basic sciences and the clinical practice of medicine. Pharmacology in industry actually does just that, much as it does in teaching. In teaching we try to correlate what the students learn in physiology and biochemistry, to add to that the action of drugs on body processes, and to bring to the student the action of the drugs on the normal subject and in the patient with disease.

In industry, then, the pharmacologist serves a somewhat similar function, correlating the work of the chemist who has developed new synthetic compounds, with the work of the clinical division. It is the job of the pharmacologist to bring out and develop new drugs which may be of further benefit to the ill patient. In doing this work, the pharmacologist works closely with the chemist. A chemist may make hundreds of compounds in a single area of study and a pharmacologist has to evaluate them. Thus we get into the first phase of the work of the pharmacologist in industry.

I would like now to mention briefly some of the things that the pharmacologist does in the pharmaceutical industry, because as we shall see later there are other types of industrial pharmacology. The pharmacologist must first set up a screening program within a given area of work. This may be the study of analgesic effects, the study of antibiotics, the study of new tranquilizer drugs, of atherosclerosis, or of hypertension. He then takes his knowledge of the area and consults with others and tries to set up the best possible method for evaluation of these new chemicals. He teaches the techniques he wishes used to technicians who will do the actual screening for him on a fairly routine basis. He will supervise their work, make sure it's done accurately, and help them when they get into trouble with the various techniques. He may find activity in one out of a hundred drugs and may study this drug further, finding out it is not potent enough. Another drug may be potent but the effective dose of the compound may be too close to the LD_{50}. So that although numerous drugs may be screened, it is only relatively few in any area that come close to a clinical trial. The pharmacologist working in this one area takes his most active drugs and discusses them with other pharmacologists. If the drug appears interesting it is developed further. He wishes to know the effect of the drug. He wants to know the effect on the heart (electrocardiogram), looking then for possible untoward effects, effects on endocrine structures, effects on blood pressure, and effects on bronchial smooth muscle. All possible undesirable effects of the compound have to be ruled out and evaluated.

Now the pharmacologist is not alone. He claims to be an expert in his own area of work, much as the teacher is an expert as regards his own research. The field of pharmacology is so large that no one person can work in but more than a few areas of pharmacology. So the pharmacologist in industry is not alone; he consults with other pharmacologists as the compound becomes of more interest. They work together on it and eventually publish on the compound or series of compounds.

In addition to this screening work, because that would be quite routine, the pharmacologist also carries on basic research work and this is done in every major pharmaceutical house in the country. Usually the basic research that the pharmacologist undertakes is a problem entirely of his own choosing. Very often the pharmacologist may do basic work in his field of screening. If he is interested in screening diuretics and is working in that area, he very often will find his research will be in the field of renal pharmacology. Other men, however, will branch out into other areas of research that are not connected with their screening program at all. In other words, the program is kept as academic as possible from the research standpoint. You will find, too, in pharmaceutical companies, men just doing basic research and no screening. They may be working on the deposition of cholesterol in the arterial wall, for example. A number of laboratories are now adding psychologists to their staffs--experimental psychologists, men familiar with reactions of animals. We have learned that there has been a whole area here that we in pharmacology know nothing about. On the other hand, the experimental psychologist is not familiar with drugs and now we have brought these two areas together and are developing psychopharmacology.

So then the pharmacologist in industrial work does two things: routine screening work and basic research. No new drug is the result of the work of one

man, but rather the work of many people consulting together. Broadness of training helps, also, in recognizing odd effects of drugs as they are studied in animals. An odd effect of a drug may lead to a more detailed study of the drug and the bringing out of new types of reactions and effects. As this drug develops it may reach a point where it goes into more detailed toxicity studies.

As Dr. Leake mentioned last night, toxicology is an important branch of pharmacology. Toxicology is done to a limited extent at first and in more and more detail later depending on interest in the drug. If the drug appears to be one that might eventually be marketed, a chronic toxicity study is finally undertaken wherein at least two species of animals receive the drug for from nine to twelve months to ascertain chronic toxic effects of the drug preliminary to marketing. This information is transmitted to the Food and Drug Administration as part of a new drug application and serves along with clinical evidence to show the limitations of the drug. There is one area, of course, of toxicity that cannot be predicted and this is the hypersensitivity reaction. We cannot predict accurately what drugs may cause agranulocytosis in man, or what drugs may cause another injury in the face of hypersensitivity, or a type of drug that will produce jaundice without producing parenchymal damage in the liver. There are still areas for basic research in toxicology, e.g., to try and explain why some of these things occur in man and why we cannot produce them in animals. We should eventually be able to do so in order that we can predict these toxic effects in man.

So much then for the pharmaceutical industry. Another area of industrial work has unfolded again more recently than pharmaceutical work. This concerns pharmacology in heavy industry. Companies like Dow Chemical, American Cyanamid, etc., maintain extensive toxicology laboratories whose work differs from the type of toxicology done by the pharmaceutical industry. They study chemicals used in heavy industry, atmospheric purity from the standpoint of inhalation of vapors and of dusts; this is done in complicated apparatus by exposing animals to minimal concentrations over long periods of time. One of the problems of the chemical industry is the labeling of materials for interstate commerce. If sacks of chemicals or barrels of chemicals are shipped into a new state they have to be labeled as to certain precautions with classification of toxicity so that if anything breaks, if dust gets on the man who is unloading the freight car, one will know if that exposure to the dust that he is receiving is safe. Toxicology, then, in heavy industry is an important phase of that type of work and handling of these materials. It is also important in synthesis, of course, in relation to exposure of the workers in any given unit.

Now, heavy chemical industry has reached out into other areas of pharmacology that have not been discussed so far at this meeting. Other companies are studying the effect of drugs on metabolism of insects. Pharmacology, as we pointed out earlier, is a broad subject. It covers the action of drugs on living cells. Insect pharmacology is a new special branch of pharmacology that is important and a number of laboratories have big programs going to study the effect of chemicals in this area. The effect of chemicals on plants is also coming into its own, requiring, of course, specialization so as to know the effects of certain chemicals on weeds and beneficial plants.

Another large area of pharmacology is related to animal husbandry. One of the great and growing problems of our day is, of course, population and food intake or food supply. There are means now of increasing the amount of protein on the animal carcass, of getting a faster growth of the animals, of getting a more economic consumption of the food of the animal and the transfer of this food into actual tissue of the animal. Again a number of these chemical laboratories have pharmacologists who are now in association with veterinarians to study this type of drug effect. The field of antibiotics in general has gone beyond the use of antibiotics in the treatment of infections in man. Antibiotics, by influencing the bacterial flora of certain species of animals, have again caused changes in usage of food affecting consumption and weight gain of our domestic food animals.

The phases I have described so far, pharmacology in the pharmaceutical industry and heavy chemical industry, insect pharmacology, plant, etc., usually require the use of pharmacologists with advanced degrees, the man with the Ph.D. and, to a lesser extent, with the master's degree.

Another area of pharmacology, of application of pharmacology, is in the performance of library information or coordination type of work, wherein the person involved may work within a group in an industrial laboratory to correlate certain facts of data. He spends his time as part of a group, going over the literature so as to find out all that is known about a type of compound, bringing out relationships of activity to chemical structure, where they can be found, toxic effects, and active clinical usefulness. It's a library information-coordination type of work. It demands a good deal of broad knowledge on the part of the person working in this area. In general it tends to lead to a semi-administrative, semi-research type of work. The person involved in such work at the present time may have the bachelor's degree, the M.S. or the Ph.D. It is a new area of endeavor for people in pharmacology. There are others in it, also, usually as part of a team. In an investigative team of this type would be a pharmacologist, a clinician, and an organic chemist so as to cover all aspects of a given topic.

There are also private industrial or private research laboratories that may employ pharmacologists. Research now is an expensive undertaking and in general only the larger pharmaceutical companies have adequate research staffs. There are a number of smaller companies without these facilities who will often turn to private laboratories for studies of pharmacological action of drugs or for the determination of toxicity. There are openings for pharmacologists in these private organizations.

Government work has not been listed but there are, of course, openings in government areas wherein pharmacologists are used.

A career in pharmacology, then, depends on broad training. This, I think, should be the goal of graduate training programs in the various academic departments of pharmacology. It is important to take men who are interested in research and point out to them the advantages of a career in pharmacology, and the scientific viewpoint it offers. Certainly there is no dirth of positions available whether the man be interested in teaching or other types of endeavor.

THE USE OF PHARMACOLOGY IN DETAILING

Howard M. Bilden

Ciba Pharmaceutical Products, Inc.

Dr. Orr's invitation to speak at this Teachers' Seminar of the American Association of Colleges of Pharmacy was accepted without critical self-analysis. I failed to ask, "Am I the most competent person for this assignment?" I was flattered when Dr. Orr told me that my name was suggested by Dean Zopf with whom I have had many interesting off-the-cuff discussions during my visits at the University of Iowa College of Pharmacy. But--when the full impact of my responsibility finally seeped through--I realized that glib remarks to an audience of one was quite a different situation compared with a talk before an audience of educators.

I have been so brash as to make critical statements about the pharmacy curriculum. I have expressed the opinion that it was not keeping pace with present-day needs. This was based on casual observation, but I knew that most pharmacists who became detail men were not equipped to easily pick up information on new therapeutic agents being sold by the drug manufacturers. New pharmaceutical developments have changed the educational requirements of practicing pharmacists, and even 25 years ago I learned that the pharmacist who decided to sell drugs for a manufacturer had to supplement his education by intensive study to qualify as a well-trained and competent detail man. The problem is much greater now.

When I was interviewed for a job with Ciba, it was explained that "Digifolin" was one of our best sales contributors and was therefore scheduled for intensive detailing. Then I was asked, "What do you know about the action of digitalis?" I answered this quickly and easily, "It slows and strengthens the heart." That is all I knew about its action--of course, dosage regulation had been thoroughly drilled into us. The interviewer, a pharmacist, did not appear surprised at my lack of knowledge and assured me that before turning me loose on the medical profession, Ciba would see that I was thoroughly indoctrinated. In training, I learned about congestive failure, auricular fibrillation, heart block, digitalization, the Bundle of His, and the role of digitalis in treating heart disease. But I did not learn then how to use this information. That came later--the hard way--and with some embarrassment because not all of the doctors in my territory were kind and understanding with a green detail man.

The "Use of Pharmacology in Detailing" is the subject assigned to me. The fact that you picked the subject indicates that you believe pharmacology is a basic requirement in pharmaceutical detailing or selling. I agree with you. Therefore, we start off in full agreement on a major principle.

Before getting into the assigned subject, I would like to emphasize that detailing is the most productive method of selling pharmaceuticals but it is the most expensive one. The American Medical Association engaged market researchers

to study the relative value of advertising and other methods of drug promotion. The published results showed that 44 per cent of the doctors who used a new drug for the first time did so because they learned about it from a detail man, 22 per cent because of direct mail advertising, and 11 per cent because of journal advertising. As the cost per detail is much greater than contacts by mail or journal ads, we strive to increase the effectiveness of our detail men by education, by producing better literature for them to use, and by more thorough territorial planning and coverage.

The A.M.A. study confirmed our opinions and observations. We had noted that vacant territories do not show sales gains--in fact, increased advertising in these areas failed to maintain sales at a satisfactory level. But, we can see sales come back and continue to grow in such territories when filled by a good, well-trained representative.

The last decade has been a period of dynamic growth in the entire drug industry, and the character of the business has changed. Fifteen years ago prescription sales accounted for only 11 per cent of total drug store volume. Last year, with business at much higher level, prescriptions accounted for slightly more than 25 per cent of drug store sales, and 63 per cent of the net profit of the average store.

In a period of expanding economy, the pharmaceutical manufacturers have reinvested 6 per cent of every sales dollar in pure and applied research. This program has proven productive; more productive than retail druggists and the medical profession like at times. However, our industry recognizes that product duplication is unprofitable to the manufacturer and to the pharmacist. Yet, in a land of free enterprise, it is a privilege to market and sell products that come from uninhibited research.

I am sure that you have seen this statement and I quote Dan Renick, publisher of American Druggist, who said, "The number of new specialties introduced 15 years ago came to about 95 per year. The number introduced last year totaled 550." That statement appeared in 1955. In another industry report, Paul deHahn showed that in 1948, 80 firms introduced 399 new products. In 1950, 100 firms put 326 new products on the market. In 1951, 86 companies came out with 321 items. In 1952, 89 firms contributed 314 new products. In 1953, 107 houses introduced 353, and in 1954, 101 manufacturers made 380 new drug products. These figures do not include all of the new dosage forms of drugs already on the market which may partly account for the differences in deHahn's findings compared to those reported by Dan Renick.

We therefore note that approximately four hundred new products hit the market each year. Some of these are so-called "wonder drugs" and may be classed as important medical contributions. Others never develop into large volume producers, yet among these are very important drugs which manufacturers often refer to as "prestige drugs." They are life-saving drugs that are extremely valuable in less frequently seen diseases. For example: a drug for the detection of pheochromocytoma has limited application and little commercial potential but--it is important. A hormone indicated for Addison's Disease will never be a great commercial success but--it is important to the unfortunate patient with a suprarenal cortex

deficiency and to the physician who is treating that patient. The drug manufacturer has a moral obligation to market these life-saving products of research even though they are devoid of sales potentials.

Obsolescence is another factor that is especially peculiar to our industry. Before World War II the average commercial life of a drug product was 11 years, but a new discovery today may be obsolete in less than two years because something better has been found.

It is important to consider the four hundred new drugs per year because they present new pharmacological problems that the detail men must know about. It is true that new anticholinergic drugs are similar in many respects to atropine. The action of histamine was known so it is not difficult to relate the effects of antihistamines to information that is available. However, a new series of drugs affecting blood pressure creates new pharmacological problems for the detail man to master. But, even here certain basic pharmacology comes into the picture. So we see that our representatives must know more about more drugs, and our industry must see that factual information about these drugs is brought to the medical profession. We recognize that untrue and overexaggerated claims will lead to disappointments and ultimately to complete loss of confidence. It is therefore necessary to honestly evaluate drugs, to be honest in what we teach our salesmen and they must be honest in what they say. That is our responsibility.

"Drug Topics" recently reported a shortage of pharmacists. I am sure this is not news to you because you probably hear this frequently. Shorter working hours and increased business have increased the demands for trained personnel. Industry's needs for pharmacists have increased, too. We look for pharmacists to detail our products, but we are unable to fill our territories with men who have a B.S. in pharmacy. We want representatives who have this background in addition to high sales aptitudes.

Pharmaceutical companies now employ twice as many representatives as they had working for them in the immediate postwar period. It has been estimated that there are 17,000 pharmaceutical salesmen (including detail men) in this country. A quick estimation that I made gave me a figure of 8,000 detail men working for 17 drug companies. Not all of them are pharmacists or pharmacy graduates, so it has been necessary to compromise. At Ciba, we specify that the man we hire must be a pharmacist or the equivalent, which may include pre-med, one, two, or three years of med school--but he must have the basic sciences. A formalized organization to train detail men in the fundamental background subjects needed to detail our products intelligently is a very recent addition to our home office personnel and as the shortage of pharmacists has grown more accute, we have raised training standards. Our staff now consists of a training director and four assistant trainers who spend full time on this job. In addition we have full cooperation of medical and research personnel who lecture on medical and scientific subjects. Training that we give in pharmacology has improved but at this time it has probably been oversimplified. To supplement the personal appearances of our pharmacologists at training seminars, we use motion pictures, film strips, "visual cast" flop-overs, and selected reading material.

Why all this fuss about pharmacology? We can prepare a "canned" detail that contains all the information which a representative need only memorize. In that way the company plans the detail, and the man, with no background, simply recites his little speech and we are sure that it is factual--if used as written. Unfortunately the "canned" or memorized presentation is easily recognized. It lacks conviction and the representative, unable to hide his meager background and lack of understanding of his subject, fails to gain respect and may be denied further visits.

Last December, when I visited my old territory in Minneapolis, I had a very interesting discussion with two of my friends. One is now practicing pharmacy after many years of detailing experience; the other is also an experienced detail man. The druggist commented about the new crop of detail men and that many of them were unable to give him good information about their products. My salesman friend told of an interview with a doctor he had called on for many years. During this particular visit the physician interrupted the detail more than usual by asking questions. Finally the detail man said, "Doctor, what are you trying to do to me? You have never questioned me like this before. Is there something wrong?" The doctor replied, "I wanted to see what happens when I interrupt an old-time detail man. These new fellows have to start all over again--as though they had memorized the stuff."

A detail man must be confident; his story should be brief and yet complete enough so that a doctor has enough information to use a new drug properly. The pharamaceutical salesman must know how a drug acts in order to describe its features and he must never fail to include the limitations and side effects, if there are any. A detail man should not attempt to teach pharmacology. But he should be able to discuss site of action, the pharmacological effects and clinical results that can be expected with his company's products and to understand the action of competitive products. Furthermore, he has more frequent need for good background these days because more physicians have had the benefit of improved training in pharmacology.

I think I can best demonstrate what a detail man is given in his training in pharmacology by looking at a specific drug. The pharmacodynamics of an antihistamine will be used as a case in point.

Our salesmen are required to study all available data on "Pyribenzamine" and they are examined to be sure that we have succeeded in our efforts to give the information. They study data on toxicity, both accute and chronic, and on absorption rates. They learn of tolerance to the drug and specific antihistamine properties <u>in vitro</u> and <u>in vivo</u> are stressed. The <u>in vivo</u> studies cover the effects of PBZ in histamine asthma experiments, histamine shock, action on bronchial muscles of the dog and circulatory studies on dogs and cats. Starling heart-lung studies, effect on intestinal motility as well as action on salivary, lachrymal and gastric secretions are included. Eye studies including nictitating membranes and pupillary dilation are also checked.

The histamine asthma experiments illustrate, in a very convincing manner, the protective qualities of "Pyribenzamine" against the offending agent in allergy. It is observed that the disturbances due to inhalation of histamine

vapor leads to asthma and shock after only one to four minutes and that these reactions were prevented or ameliorated by adequate quantities of previously administered drug.

Such information dealing with specific antihistaminic properties gives the representative a better appreciation of the effectiveness of the drug. When these studies are confirmed by clinical experience, he is confident of his ground and he can talk with physicians about "Pyribenzamine" with conviction. He recognizes limitations and is aware of possibilities of failures, side effects, and toxic reactions. He will understand the comparative virtues of competitive drugs. Once convinced that the drug he is selling is effective and it has a useful place in medicine, the representative is then prepared to give a good presentation.

How much of this information should he use and how shall he use it? Obviously the detail man must be sensitive to the reactions of his audience and use only as much of this background material as is necessary and no more. Some physicians want to explore a new product thoroughly while others only want to know: What is it? What is it used for? and, How is it given?

It is important though to have complete information so that questions can be answered on the spot. We insist that a representative never attempt to guess the answer. If he does not know, he should admit it and offer the services of our medical department. This not only makes a better impression than a vague half truth or even a falsehood but a letter from one of our doctors a few days later may serve as a reminder of the discussion with the detail man.

Few representatives are deliberately dishonest in their statements to physicians. Most part truths are made by the poorly informed who are unaware that products are being misrepresented, because they lack the background that would affect their judgment.

I pointed out that there are many pharmaceutical detail men calling on physicians who are often so busy that they are reluctant to give up valuable time to salesmen. However, we are convinced that they will generously give their time to detailists who can keep them posted on new therapeutic developments. Many doctors depend on this source for information and the competent man can save time by well-presented details on drugs that fill a need. By that I mean know the doctor's specialty or specialized medical interests and detail only products that fit the specialty. Baby foods or drugs for pediatrics are of no interest to a urologist.

It is my opinion that pharmacological training in pharmacy schools equips the pharmacist for a career in pharmaceutical selling. Demonstrated abilities in the field of pharmaceutical detailing will provide job satisfaction and opportunities for advancement in an expanding industry.

OPTIMUM PREREQUISITES FOR THE UNDERGRADUATE COURSE IN PHARMACOLOGY AND TOXICOLOGY

Troy C. Daniels

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Preliminary to a discussion of the prerequisites for the study of pharmacology, it is desirable to give some consideration to the nature of the subject, particularly with reference to its scope and the basic sciences necessary to nourish its development. Goodman and Gilman define pharmacology as including "knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate and excretion, and therapeutic uses of drugs." Schmiedeberg on the other hand defines pharmacology as "an experimental science which has for its purpose the study of changes brought about in living organisms by chemically acting substances (with the exception of foods) whether used for therapeutic purposes or not." Some prefer to think of pharmacology in a more restricted sense as involving the "response of living cells to chemical stimuli." Irrespective of the definition agreed upon, it should be recognized that the scope of pharmacology is extremely broad and that it embraces the physical and biological sciences at a comparatively high level.

The action of drugs on cells is determined in part by the rates of a number of reactions believed to take place sequentially or simultaneously. The action is also determined by the physico-chemical properties of the drug, the shape of the molecule and by the types of functional groups present. Many of these properties and the mechanisms of the reactions they affect can and should be treated mathematically, and it is, therefore, not surprising to find mathematics playing an increasingly important role in the design and interpretation of biological experiments. Living cells vary in their response to chemical stimuli and statistical methods should normally be used in planning and interpreting experiments involving the measurement of drug action. Mathematics through elementary calculus may be regarded as an important background and a logical prerequisite for the study of advanced pharmacology, but calculus and statistics are not essential for the undergraduate course as it is generally offered. However, mathematics through calculus is a prerequisite for physical chemistry, knowledge of which can contribute immeasurably to the study of pharmacology.

Physical Sciences

Pharmacology, in a major respect, involves the application of physics and chemistry to biological systems, and the significant role these two basic disciplines have played in the development of pharmacology cannot be overemphasized. To illustrate the importance of these basic sciences in pharmacology, it should be remembered that most pharmacological experiments involve some aspect of applied physical chemistry such as: the control of pH; use of buffers; absorption spectrophotometry in the ultraviolet, visible, and infrared regions of the spectrum; ion exchange resins; polarographic methods; oxidation-reduction potentials; countercurrent extractions; radiochemistry, etc. Applications of physical chemistry have

made possible such discoveries as the existence of nor-epinephrine in extracts of the adrenal medulla, the distribution and separation of the active constituents of crude drugs, study of the metabolic changes drugs undergo in the body, and many other contributions in pharmacology.

Now with this generalized statement as to the nature of pharmacology, I would like to outline the prerequisites for the undergraduate course.

There are at least two major areas in the physical sciences that may be regarded as logical prerequisites for pharmacology; namely, physical chemistry and organic chemistry. In focusing our attention on these two areas, it should be kept in mind that in order for them to be presented at an adequate level each must have its own prerequisites.

In the case of physical chemistry, the prerequisites normally include mathematics through elementary calculus, physics (8)*, general chemistry including qualitative analysis (10), and quantitative analysis (3-5). The physical chemistry should include a minimum of six units and be offered as a year course. An elementary course in organic chemistry (9-10) falls short, in my opinion, of giving an adequate background for the study of pharmacology. Pharmacy students are fortunate in having corollary courses in pharmaceutical chemistry such as the chemistry of natural products, synethsis of medicinals, drug analysis, etc., which serve to strengthen their background in organic chemistry and prepare them to think in terms of the relationship of chemical structure and the physical properties of molecules, which is a preliminary step to thinking in terms of chemical structure and biological properties.

Biological Sciences

The pharmacy curriculum offers an excellent background in the physical sciences for the study of pharmacology but unfortunately this is not true with respect to the biological sciences. In general, the schools of pharmacy have been remiss, if not grossly negligent, in the treatment and development of the biological sciences in the curriculum. Pharmacology is an extremely important subject for the pharmacist and represents the culminating or climax course in the sequence of courses in the biological sciences. Unless these background courses are developed at a level that leads to an understanding and appreciation of the biological principles involved, the course in pharmacology tends to become a course in *materia medica.* Pharmacology is recognized as the common meeting ground of pharmacy and medicine, and a comprehensive knowledge of this subject is essential for the pharmacist to discharge his professional responsibilities. In a major respect, the future of pharmacy lies in pharmacology, and we must not allow the biological sciences in the curriculum to remain *status quo*. You may be interested in the definition of *status quo*, as given by a southern pastor in addressing his flock, which, as he explained, means "the fix we're in." The schools of pharmacy have been in a "fix" with respect to finding the curriculum time necessary to develop the biological sciences in proper sequence and

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*Figures in parenthesis are semester units of credit at the University of California.

at an adequate level. This time element will be relieved somewhat with the adoption of a minimum five-year program of education, but the problem will not be fully resolved until there is reasonable agreement on what constitutes the optimum prerequisite program for the study of pharmacology. The problem relates not alone to the subjects involved but more importantly to the extent and level of instruction that should be required in each area.

The following prerequisites in the biological sciences are recommended for your consideration:

1) General Biology, Botany, and Zoology (8-12)

In the pharmacy curriculum, botany is a prerequisite for pharmacognosy, and many colleges and universities combine the elements of botany and zoology into a single course known as general biology. An understanding of life processes of plants and invertebrate and vertebrate animals, including some comparative anatomy and physiology, is quite generally regarded as an essential prerequisite for human anatomy and physiology. Where it is possible, it may be desirable to separate botany and zoology and require a four-unit course in botany (lectures and laboratory) and eight units of zoology (lecture and laboratory). I am informed by those competent to judge that zoology cannot be adequately presented at less than the eight-unit level. If this is true, the course in general biology may not offer adequate preparation for anatomy and physiology and perhaps consideration should be given to consolidating botany and pharmacognosy into a combined course (8-10 units) in which the botany precedes the pharmacognosy. In this way, a year course in zoology might replace the one-year course in general biology. Zoology and botany are frequently unpopular subjects with students but this is not due to an inherent irrelevancy of the subject matter which is essential. The objections are probably due to the necessity of acquiring new vocabularies and failure to appreciate the value of the laboratory work.

2) Anatomy and Histology (5-6)

With zoology as a background, the pharmacy student should be given a course in human anatomy with emphasis on the functional as well as the morphological aspects. Ideally, the subject should cover the following: prenatal and postnatal development; the histology of the important tissues such as the heart, liver, brain, kidney, etc.; the skin; bones and joints, including their arrangement; striated and non-striated muscles; nervous system; circulatory systems; vascular systems; respiratory and alimentary systems; genitourinary system; and the endocrine glands. The anatomy instruction can be offered in a single semester, but pedagogically it is desirable to offer a year course. Student time in the gross laboratory may be conserved by making judicious use of prosection material, in which case a cadaver may be sufficient to accommodate the needs of as many as six students. At the five-unit level, the course should consist of three lectures and six hours of laboratory and, if a six-unit course is offered, another three hours of laboratory may serve to best advantage.

Physiology (6)

Physiology is universally recognized as an essential prerequisite to pharmacology and the importance of this subject can scarcely be overemphasized. The student needs first to gain an understanding and appreciation of the normal functions of cells, tissues, organs, and the various systems of the body as a background for an understanding of pharmacological principles. Emphasis should be given to human physiology in the lectures, and the laboratory experiments should deal primarily with experimental animals. In connection with this, it should be remembered that, for the most part, pharmacology makes use of techniques that were first introduced in physiology, physical chemistry, and biochemistry--it has few techniques of its own and, therefore, it is important for the student to become familiar with the use of these techniques prior to conducting laboratory experiments in pharmacology. The six units of instruction recommended should consist of four units of lecture and two units (six hours) of laboratory work. This is a minimum requirement and may well fall short of the ideal. Some physiologists believe human physiology requires a minimum of six units of lecture and three units of laboratory work, in which case the instruction would have to be given as a year course. The anatomy instruction develops the gross and morphological background for an understanding of the dynamic processes of the living body studied in the physiology course.

Biochemistry (4-6)

Biochemistry deals with the chemistry of living things and, therefore, represents an extremely broad branch of chemistry, embracing inorganic, analytical, organic and physical chemistry. Biochemical techniques are widely used in pharmacology, the study of which is generally recognized as requiring biochemistry as an essential prerequisite. Normally at least six units of instruction in biochemistry (four units of lecture and two units of laboratory) are required for medical students, but the pharmacy student has a much more comprehensive background in chemistry than the medical student and a great deal of the laboratory instruction is covered in ancillary courses. Therefore, the standard laboratory instruction may be regarded as optional. If time permits, however, two or more units of special laboratory instruction for pharmacy students would serve a most useful purpose.

Microbiology (6-8)

A comprehensive course in bacteriology and parasitology, with some consideration given to mycology, may be regarded as an essential prerequisite for the study of chemotherapy in pharmacology. It is unnecessary to outline the objectives of instruction in microbiology for they are relatively standardized and well understood. However, microbiology for the pharmacy student should place emphasis on the disease-producing or infectious microorganisms. Some institutions prefer to separate parasitology and mycology from microbiology, in which case a five-unit course consisting of three units of lecture and two units of laboratory may be assigned for microbiology and three units (two lectures, one laboratory) assigned to parasitology including dermatophytic and other pathogenic fungi. The subject matter of these courses should precede the course in pharmacology.

Pathology (4)

Pathology is a normal prerequisite for pharmacology in most medical schools and serves as an excellent background for the study of drugs. In general, the subject covers the processes by which diseases become established in the human body and the various compensatory mechanisms by which the body resists the disease process. It includes also the study of pathological anatomy and pathological physiology and it is, therefore, essential that normal anatomy and histology and normal physiology precede the instruction. The prerequisites for pathology are anatomy and histology, physiology, and biochemistry. Microbiology should also precede or may be given concurrently.

We have had several years of experience with pathology in the pharmacy curriculum and it has received most favorable student acceptance. The course at the present time consists of two units of lecture and two units of laboratory work and although at the present time it follows pharmacology, it will soon be possible to establish the course in its proper place as a prerequisite. Pathology serves a most useful purpose in familiarizing the student with medical terminology and in integrating the instruction in the biological sciences in terms of "distinct medical entities." A summary outline of the topics covered in the lectures is attached for your information.

Pharmacognosy (4-6)

Historically, botany and pharmacognosy have played a leading role in pharmacy education. At one time a large percentage of the drugs in use were derived from plant sources and some of our most useful drugs are still obtained from these sources. With the successful development of synthetic organic medicinals, the leading role oncc staged by botany and pharmacognosy has been somewhat overshadowed. However, within the last decade, there has been a marked resurgance of interest in drugs of natural origin.

Pharmacognosy should follow anatomy, physiology, and the chemistry of natural products and should serve to integrate and consolidate the subject matter of these courses that is pertinent to the application of drugs of natural origin. Pharmacognosy provides a most useful stepping stone to pharmacology.

Pharmacology

With the prerequisites outlined, the undergraduate course in pharmacology can be presented in a much more meaningful and effective manner. The course should be offered as a year course in the third year of the professional curriculum, and in a four-year professional curriculum additional courses in pharmacology and toxicology can be added to advantage.

In summary, I should like to emphasize that a comprehensive background in both the physical and biological sciences is necessary for the profitable study of pharmacology. In an increasing number of the schools of pharmacy, an adequate background in the physical sciences is now offered. This is not true in the biological sciences which need to be substantially strengthened. With the adoption of the minimum five-year program of education, it will be possible to

increase the amount of time in the biological sciences and improve the students' background for the study of pharmacology. When this is accomplished, the schools of pharmacy will be in a more favorable position to nourish pharmacology than the medical schools where there is but little opportunity to develop the physical sciences at an adequate level. In this regard, I should like to point out that many, if not most, of the excellent contributions in pharmacology that have come from laboratories in Europe stem from the application of physico-chemical methods and principles to pharmacology and this undoubtedly is the primary reason for their pre-eminence.

The pharmacist needs to be the best qualified person to give the medical practitioner advice on the physical and pharmacological properties of drugs and in order to achieve this objective, pharmacology must receive increasing attention in the curriculum. The future of pharmacy as a profession lies largely in the domain of pharmacology and I am, therefore, confident that it will not be allowed to wither on the academic vine.

PHARMACOLOGY IN THE PHARMACEUTICAL CURRICULUM OF THE FUTURE

John G. Adams

Duquesne University

The oft-quoted phrase from Scripture, "Old men shall dream dreams and young men shall have visions," may offer the chronological, if not reasonable, explanation for my presence before you this afternoon to discuss "Pharmacology in the Pharmaceutical Curriculum of the Future." As a rather young and inexperienced pharmacologist, and perhaps more important in terms of the pharmacy curriculum, a young and inexperienced dean of a pharmacy college, I am more interested in the future than in the past. It is for this reason that I gratefully and to some extent temerariously accepted the invitation of the Seminar Committee to gaze into the crystal ball of pharmaceutical education to predict the importance and the manner in which pharmacology will be integrated into the pharmaceutical curriculum of the future.

A second reason for my acceptance is the knowledge that one is on fairly safe ground in predicting things to come. I offer as evidence the fact that the ancient art and mystery of crystal-ball gazing, palmistry, and the reading of tea leaves have been declared illegal in those parts of the world which are considered civilized. I am also supported and consoled in my assignment by Mr. George Gallup's prediction of the 1948 presidential election, which as many of you may recall wasn't exactly correct. What has followed since is history, and I am encouraged by the fact that Mr. Gallup is still in business. With a little introspection, I have decided that the Committee has made a poor choice in spite of my youth, for I have never been successful in predictions. If I had been, I doubt whether I would be either pharmacologist or dean. My days would be spent at the New York Stock Exchange, the Santa Anita racetrack, and Monte Carlo, and my nights drinking chloropromazine cocktails to soothe my ire over income taxes. Incidentally, I didn't check with Dean Orr about local ordinances governing fortunetelling, but since the thought occurred to me, I have decided to insist that he explain the item on my expense account which reads, "Fine for violation of Local Ordinance No. 10, entitled, 'Palmistry, witchcraft, and similar offenses' - $100."

In spite of some rather obvious levity and frivolity about my subject, I think you will agree that my assignment is not an easy one. As a matter of fact, it is a very difficult one as any dean or faculty member in the country engaged in curriculum studies for the extended program can attest. Your speaker has two stated assignments. One is to predict the pharmacy curriculum of the future, and the other is to predict the position and importance of pharmacology in that curriculum. There is actually a third part to the assignment which although not so apparent, is just as real, and that is, of course, the future of pharmacology. Unless my meager knowledge of variables and functions has failed me, I seem to recall that in a three-component system in which there are three possible variables, one value must be held constant, in order to establish values for the

other two variables. On this basis, my assignment is not only difficult--it's impossible. However, since I was foolish enough to accept the assignment, I will remember the famous slogan of the U.S. Army Air Forces, "The difficult we do immediately. The impossible takes a little longer." I have been working on the impossible since Dean Orr's Committee extended its invitation some six months ago.

I stated a few minutes ago that I was more interested in the future than in the past. Every participant in this seminar obviously has the same interest. But just as our interest is in the future, we must all recognize that our heritage is in the past and our accomplishments are in the present. The importance of a knowledge of history, and I refer at this moment to the history of pharmacy and of pharmacology, was forcibly brought to my attention when it was my good fortune to work in the same laboratory with Dr. Bruno Minz, a name well known to pharmacologists. In discussing some of his work, including dorsal leech muscle preparation for measuring acetylcholine activity, he very convincingly proved to me that his discoveries were neither unique nor original, but were based on information which had been gathering dust in the literature for years. As I worked with Dr. Minz, I observed in his research what appeared on the surface to be a kind of pharmacological insight, but in the hidden depths, was a profound knowledge of his field. I suspect that Dr. Minz and others of his ilk, would in modesty protest that much of success in research is luck--a kind of shot-in-the-dark proposition--which I cannot deny does contain an element of chance. But I, for one, am convinced that this kind of luck is calculated through years of diligent preparation for taking advantage of the breaks when they come. There is a moral to this story which is related to my subject in the event I have digressed too freely. Any kind of prediction, whether it be of tomorrow's weather or of the future of pharmacology in the pharmacy curriculum, is based on the past and present, and it might be apropos for me to briefly consider the backgrounds of both the pharmacy curriculum and pharmacology before I hazard any guesses about the future.

In the early history of pharmacy and pharmacology--and history is about the only basis for using the terms in relation to pharmacy and pharmacology as we recognize them today--the two disciplines were mutually inclusive, as were the other basic science areas of pharmacy and medicine. The first significant departure occurred with the division of labor between the role of the physician and pharmacist--a division which still isn't as sharp as it should be at least on an ethical basis. The edict of Frederick II of Sicily in 1240 might conceivably be considered a convenient if not the actual starting point for establishing distinct roles for pharmacist and physician. The function of the physician was to diagnose and prescribe; that of the pharmacist, to compound and dispense the medications so prescribed. Prescribing of drugs by the physician and compounding and dispensing drugs by the pharmacist required that they both have a knowledge of drugs.

As you well know, it hasn't been too long since the term "materia medica" was as common in the medical curriculum as it was in the pharmacy curriculum. I would venture a guess that there are still quite a few practicing physicians who could correctly identify deadly nightshade as belladonna, or Jimson weed as stramonium. Since the division of labor between pharmacist and physician,

however, there has always been a different emphasis of the application of this knowledge of drugs. Despite the inclusion of _materia medica_ in both curricula, a knowledge of the source and pharmaceutical preparation of drugs was and is primarily a point of academic interest to the physician, whereas his professional and primary interest was and is in the action of the drug and its effectiveness in treating the disease which he has diagnosed. The _materia medica_ of pharmacy placed the professional and primary emphasis on the source and/or the manufacture of drugs and their incorporation into suitable dosage forms. A knowledge of their action and use was one of mere academic interest.

In recent years, there has been a decided emphasis placed on pharmacodynamics and therapeutics by the physician to the virtual exclusion of a knowledge of the source and preparation of drugs currently used in therapy. The emphasis on source and/or manufacture of drugs and their incorporation into suitable dosage forms by pharmacists remains essentially unchanged in spite of the growth of a giant pharmaceutical industry, which compounds on a mass production basis the prescriptions which were formerly compounded _secundum artem_ in the _sanctum sanctorum_ of the prescription room of the neighborhood drug store--and I might add much less scientifically and certainly less elegantly.

Just as there has been a waning of interest in the pharmacy of _materia medica_ by the physician, there has been an avid and enthusiastic interest shown in pharmacodynamics and therapeutics by the pharmacist, this interest having developed as a result of the tremendous advances made in the treatment of disease in the past fifty years. It might be well to point out before proceeding, that in spite of shifting emphasis and interest on the part of physician and pharmacist due to causes most of which are known to you, and one of which I have indicated, the basic responsibilities and functions of both practicioners of the health sciences remain the same. The physician diagnoses and prescribes; the pharmacist compounds and dispenses.

If one examines the pharmaceutical curriculum from the time of the establishment of the first chair of _materia medica_ at Salerno to the present, he will discover that the objectives of the pharmacy curriculum have always been designed to train the pharmacy student for the responsibility and function delineated above; that is, the compounding and dispensing of drugs. It is quite true that the content of pharmaceutical curriculum as we know it today is vastly different from that of most schools as little as 25 years ago. But the objectives remain the same. And, similarly, the objectives of the medical curriculum remain the same in spite of vast changes in content. I might even say that the basic content, while modified as a result of division among the basic and professional courses, for example, pharmacology and pharmacognosy from _materia medica_, remains essentially the same or has since the latter part of the eighteenth and early part of the nineteenth century. If one accepts this interpretation of the history of pharmaceutical curriculum, and I believe I have guarded my statements carefully enough to prevent too serious a protest, then I have reached the first plateau of the "$64,000 Question." Before gazing into the crystal ball, however, a brief resumé of the place of pharmacology in the pharmaceutical curriculum past and present might be in order.

The history of pharmacology is inextricably bound to the now obsolete discipline of _materia medica_. To avoid a prolonged discussion, we need only trace

our steps to the year 1872 and to the persons of Oswald Schmiedeberg and his pupil, John Jacob Abel, who was the father of American pharmacology and the occupant of the first chair of pharmacology in the United States. Pharmacology became a distinct basic science during this era, and is presently defined as the science of the nature and properties of drugs, particularly their actions. It is a well-established rule of Aristotelian logic that one cannot have an honest argument about anything unless he and the others who take part in it are agreed on terms. A term, says the dictionary, is a word or phrase used in a recognized and definite sense in some particular subject. It is interesting to note that in less than one hundred years the science has already been subdivided into pharmacodynamics, pharmacotherapy, and chemotherapy, not to mention toxicology, neuropharmacology, quantitative pharmacology, therapeutics, and other subdivisions with similarly impressive titles. As a pharmacologist, and to logically present my arguments, I propose that the definition of pharmacology be confined to the science of the action of substances of any origin (natural or synthetic) on cells and tissues of plant or animal origin; that the nature and properties insofar as their sources and preparations are concerned be confined to the areas of pharmacognosy (including substances of bacterial or other microbial and/or animal origin in addition to plant products); pharmaceutical (medicinal) chemistry including industrial chemical poisons; and pharmacy.

The new and distinct science of pharmacology established by the Schmiedeberg school is or should be the basis for courses in basic pharmacology as presently taught in schools of pharmacy, medicine, dentistry, and other health sciences. Applied pharmacology, such as courses in therapeutics and toxicology, and others which might include preventive medicine and other disciplines in the medical, dental, or veterinary curricula, is not a pharmacy discipline, and thereby hangs a tale and the warning buzzer for the last round.

With this necessary but altogether too brief history of the pharmaceutical curriculum and of pharmacology as a background, it is incumbent upon the speaker, if he is to fulfill his assignment, to devote the remainder of the time allotted to a discussion of the present and, more specifically, a prediction of the future. In reference to the present, I deem it unnecessary to expound at great length the philosophy, objectives, content, and outcomes of the pharmacy curriculum. All of you present today are familiar with them and, despite minor deviations among the various schools, these factors are essentially the same in all colleges of pharmacy.

There is one point, however, which I deem worthy of consideration insofar as the present curriculum is concerned, and particularly in relation to the pharmaceutical curriculum of the future. We all recognize that in the past 25 years there has been a decided shift in the role of pharmacist as compounder and dispenser. With the rise of a giant pharmaceutical industry, the pharmacist in recent years has been primarily concerned with dispensing rather than with the compounding of drugs and medications. As noted before, this, in my opinion, is a very favorable change, for it has resulted in better standardized and considerably more elegant pharmaceutical preparations. It has, in addition, provided the most efficient drugs and drug combinations for use in treatment of disease that the world has ever known. It cannot be denied that there has been a real awareness on the part of the pharmacy profession of this shift of the compounding

of prescriptions from the prescription counters of neighborhood pharmacies to the laboratories and production plants of the pharmaceutical industry. It has been my observation, however, that in this shift, there has been a kind of panicky behavior by the profession in attempting to cope with the situation and to maintain a raison d'etre. One of the results, and one which I vigorously protest, has been the suggestion that pharmacology become the pre-eminent discipline of pharmacy. Many have suggested that the function of the pharmacist has changed from that of a compounder and dispenser of drugs to that of a therapeutic consultant to the physician. This interpretation of the change which has occurred is one that I also vigorously protest. In my opinion, the present pharmaceutical curriculum does not train the pharmacy student to assume this role. As I have indicated before, a knowledge of therapeutics is based not only on basic pharmacology but on diagnosis and pathology. The latter two disciplines, with the possible exception of schools of pharmacy offering a six-year program, are not offered in the pharmacy curriculum and consequently the graduate of pharmacy is not in a position to act intelligently as adviser to the physician in matters of therapeutics.

I recognize that there will be strong objections to the stand which I take, but I think in the final analysis, my critics will be forced to agree. In my opinion, it is entirely possible that this role may be in the offing for the future, but I reiterate that at present, the pharmacist is not trained for it. It is likewise my opinion that the role and function of the pharmacist at the present time is the same as it has been for the past several thousand years. And that role is, I repeat, one of compounding and dispensing drugs.

In the confusion which has resulted from the modus operandi of the present-day pharmacist, that is, in the change of his role as a compounder in the recent past to that of dispenser in the immediate present, a large number of pharmaceutical educators have lost sight of the true role of the pharmacist in the year 1957.

There has been increasing emphasis placed upon pharmacology and decreasing emphasis placed on pharmacy. I am fearful of the consequences unless something is done to re-define objectives and give pharmacy, as it is practiced and will be practiced in the near future, its rightful place in the practice of the health professions. The pharmacist is still the expert on the preparations and dosage forms of the drugs which are currently used in therapy, and as such can provide very valuable information to the practicing physician. He can, if properly trained in basic pharmacology, provide valuable information to the general practitioner of medicine. This information at present, however, is more academic than clinical, for it is not within the province of the pharmacist to see the patient nor to see the results of the drugs which are administerd for the treatment of the patient's illness. This is the province of the physician and will continue to be his prerogative in the years to come.

Finally, I have arrived at the heart of the matter which I was requested to discuss, "Pharmacology in the Pharmaceutical Curriculum of the Future." To discuss it, I must first gaze into the crystal ball and predict something about the nature of the pharmacy curriculum of the future, and following that, predict the role of pharmacology in that curriculum. My observations and predictions will not be unique nor original. The lesson I learned from Dr. Minz has been learned well.

Nor will my predictions be purely speculative, for they are based on trends which I have observed over the past several years, and though not a student of history, on the heritage which I have inadequately presented in earlier portions of this paper.

I predict that the pharmaceutical curriculum will continue to be primarily concerned with the training of students to compound and dispense prescriptions. The place and the manner in which these prescriptions are compounded have changed and will continue to change in the years to come, but the persons best qualified and trained for this task will be those educated in our colleges of pharmacy. I would deem it very prudent and wise of the pharmaceutical educators to bear this point in mind and design the pharmaceutical curriculum of the future to meet this particular need. Courses in pharmacy as presently taught will change in pattern and content as the result of the shift in compounding of prescriptions from the neighborhood drug store to the pharmaceutical industry.

The area of pharmacology will become an increasingly important one in the pharmaceutical curriculum and may, as previously mentioned, be expanded to include courses in diagnosis and pathology in order to prepare the pharmacist as a therapeutic consultant to the physician. I suspect that if this does occur, we will have to consider the re-definition of the word pharmacist, for as therapeutic consultant, the former role and function of the pharmacist will have changed so considerably that our therapeutic consultant of the future will no longer be primarily concerned with the compounding and dispensing of drugs. Rather he will be primarily concerned with the use of drugs in the treatment of disease. In terms of the patient, I think it makes little difference whether medication is suggested or prescribed by pharmacist or by physician. But in any case, it is important that in the total patient care, the patient's illness be properly diagnosed and that medications be selected on the basis of the physician's diagnosis and rationally prescribed by either physician or pharmacist on the basis of a knowledge of the disease to produce the most expeditious and efficient result possible.

I envision the role of the pharmacist in the future to be that of an expert on drugs--their sources, their preparation, and their uses. I predict a division of labor in pharmacy which will result in the training of pharmacists primarily engaged in production of drugs and drug combinations, and training of pharmacists who will be engaged in practice as therapeutic consultants to physicians. I predict that the art of pharmacy and extemporaneous compounding of prescriptions will eventually disappear from the scene and that dispensing of drugs by the pharmacist as a member of the health professions team will be coupled with his role as therapeutic consultant. In both areas of pharmacy, it will be necessary that the student be trained in a basic knowledge of pharmacology. As a member of the pharmaceutical industry, it will be critical that the pharmacist be thoroughly familiar with experimental (academic) pharmacology in addition to preparation and dosage forms. As a general practitioner, it will be equally as critical that the pharmacist be thoroughly trained in applied (clinical) pharmacology and particularly in the area of therapeutics. Such a prediction implies the inclusion of courses in diagnosis and pathology and such other disciplines as may be necessary for the complete understanding of the use of drugs in therapy.

These concentrations, I predict, will be included in the pharmaceutical curriculum of the future, but not as required courses for all persons engaged in the profession of pharmacy, but only for those engaged in practice in conjunction with the practicing physician. In planning for such an eventuality, it will be important that pharmaceutical educators constantly bear in mind the objectives of their curriculum. The division of labor between medicine and pharmacy must be maintained and, as never before in the history of the two professions, it will be critical that strict ethical conduct be observed so that the pharmacist trained in diagnosis and pathology as well as in the field of therapeutics does not usurp or interfere with the practice of medicine by physicians. In spite of his advanced training, and of knowledge in common with physicians, he is not and will not be primarily trained to diagnose and treat illness, but merely to act as a therapeutic consultant to his medical colleague.

Crystal-ball gazing is not an easy art. I have presented some provocative ideas with which you may or may not agree. I have predicted the future in reference to the place of pharmacology in the pharmaceutical curriculum--a prediction which only time will prove to be correct or incorrect.

You are no doubt aware that I have completely deleted any discussion of the future of pharmacology. My omission is by design rather than by accident and you will notice that the committee was very prudent and I might add very considerate in doing likewise. In working out my assignment, I have followed the basic rules of mathematics in holding one value constant and that value, of course, is the future of pharmacology. I suggest that we may need a new equation for predicting the role of pharmacology in the pharmaceutical curriculum of the future, but in the meantime, I will maintain my faith in Dalton's Theory of the atom which is the ultimate explanation for drug action at the cellular as well as any other level of activity. As a closing thought, I recommend that we consider the well-known fact that history repeats itself. With continued advancements in the prevention and treatment of disease, it is entirely possible that the roles of both future physician and pharmacist will be, in comparison with their present ones, reduced to a minimum and that the physician-pharmacist or pharmacist-physician will be a single entity. Anachronistic perhaps--but possible!

Tuesday Session

MECHANISMS AND METHODS IN PHARMACOLOGY

Troy C. Daniels

Chairman

BIOCHEMICAL APPROACH TO PHARMACOLOGY

W. C. Holland

Vanderbilt University

General pharmacology is a science devoted to the study of the mode of action of drugs. During its development, pharmacology relied heavily on established physiological principles in interpreting the mode of action of chemical substances on biological structure and function. For example, local anesthetics block nerve transmission, epinephrine and acetylcholine affect heart rate, etc. With the advances of modern biochemistry as a stimulus, pharmacological interest has gradually shifted from the organismic to the cellular and subcellular level. Today, we speak of drugs that depress cell permeability or inhibit certain specific enzyme reactions or those that produce characteristic changes in cell morphology. However, with the chemist discovering new biochemical reactions at an exponential rate, the science of pharmacology has reached a crisis of confusion and indecision. To resolve the difficulty, one must stop to analyze the situation; decide whether the vast number of reactions can be classified into patterns of reactions that serve some purposive or useful role in maintaining cell structure and function. It would appear that the introduction of the energy concept would best serve the needs of modern pharmacology. In order to accomplish our goal, we must first begin with a study of over-all energy metabolism in biological systems as we know it today.

Metabolism of living systems, i.e., plants and animals, is in reality only a breakdown and re-synthesis of H_2O. With the aid of certain pigments (chlorophyll) plants are able to separate water into its elements, hydrogen and oxygen, the energy for the process being obtained from sunlight. The oxygen formed is returned to the atmosphere and CO_2 is absorbed and combines with the hydrogen to form carbohydrates and other essential foodstuffs. In animal systems, the process is reversed. Hydrogen and oxygen are re-combined to form H_2O, the oxygen being absorbed and CO_2 released to the atmosphere in the process. The energy made available is either dissipated as heat or converted to work by the cell.

The latter group of reactions is much more complex than I have pictured for you. A great number of intermediate steps are involved. The great advances of modern biochemistry have concerned themselves with the elucidation of the details of the chemical reactions involved in over-all energy metabolism. In the remaining paragraphs I shall attempt to outline for you these major contributions.

Cell Metabolism

Metabolism may be defined as the chemical changes in living cells, by which energy is provided for vital processes and activities. Thus, metabolism includes both energy yielding and energy liberating mechanisms. The primary process connected with energy production is the oxidation of foodstuffs.

Oxidation of foodstuffs is a step-wise process, which being diverse for various foodstuffs in its early phase, is quite uniform as the substrates reach final stages of energy production. These reactions proceed simultaneously under the influence of a complex system of enzymes, many of which, in turn, are dependent for activity upon smaller non-protein coenzymes. These coenzymes are in large part derived from the vitamins of the B-complex and thus constitute a means by which nutritional status may influence cell function. Another important class of biochemical regulators of metabolism is the hormones which appear to exert an influence on metabolism by controlling transport of essential materials into and out of the cell.

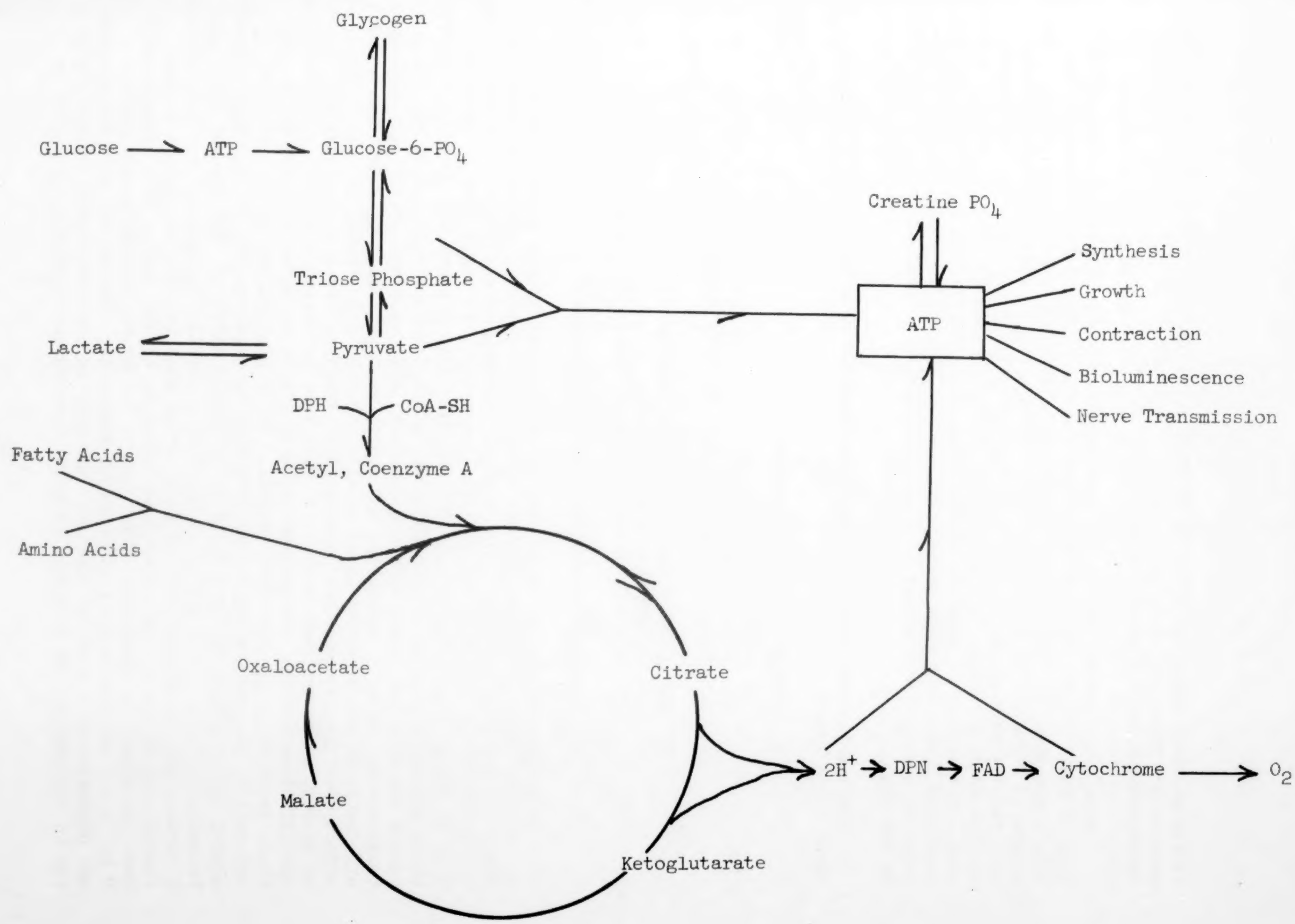
Biochemists have shown that the original foodstuffs, carbohydrates, fats, and proteins are broken down to a very simple compound: acetate. This acetate (two carbon compound) becomes activated by attachment to a molecule of coenzyme A, a derivative of pantothenic acid, to form the active acetate or acetyl coenzyme A. From this common relay state, the substrate is shunted through the main processes of energy production, the Krebs citric acid cycle, the hydrogen transport system, and the cytochromes (See Fig. 1).

During the complete oxidation in these several systems energy is made available and conserved by a process referred to as oxidative phosphorylation. In fact, it has been shown that 36 high energy phosphate compounds (ATP) are formed from the complete oxidative of 1 mole of glucose. The process is somewhat more efficient in case of oxidation of fats.

The energy trapped in these energy "rich" compounds can be stored by transfer to creatine phosphate or used immediately by some energy utilizing or convertor system. These latter systems have one property in common; the ability to convert chemical energy into other forms of energy: for example, structure (potential), motion or contraction (mechanical), concentration gradients (osmotic), bioluminescence (light), and transmission and conduction (electrical). Thus, it should be apparent that the energy utilizing or convertor systems in cells form the molecular basis of what physiologists and morphologists speak of as specific structure and function.

Unfortunately, very little is known of the chemical nature of the systems that underlie the various physiological functions such as contraction, secretion, growth, transmission, etc. Only in the case of muscle contraction do we have any idea of the chemical material involved in this fundamental process. Szent-Gyorgyi and Coll have recently proposed a new hypothesis to account for certain aspects of muscular contraction. They have concluded that the ultimate contractible unit in muscle tissue is a large protein molecule, the acto-myosin fibril which is a conjugate of two muscle proteins polymerized actin and myosin. Upon interaction of this complex with ATP the fibril changes its physical form (contracts), energy for the process being furnished by hydrolysis of ATP.

Recent investigations tend to indicate that cholinesterase, an enzyme which hydrolyzes the parsympathetic mediator acetylcholine, may be involved in cell permeability. This enzyme has been found to be located in cell membrane of the erythrocyte and certain nerves. In a manner analogous to ATP-actomyosin system, interaction of acetylcholine with cholinesterase results in a structural change


Glycogen
Glucose
ATP
Glucose-6-PO4
Triose Phosphate
Lactate
Pyruvate
DPH
CoA-SH
Acetyl, Coenzyme A
Fatty Acids
Amino Acids
Oxaloacetate
Citrate
Malate
Ketoglutarate
Creatine PO4
ATP
Synthesis
Growth
Contraction
Bioluminescence
Nerve Transmission
2H+
DPN
FAD
Cytochrome
O2

in the protein component which is evident physiologically as a changed cell permeability. Little or nothing is known of the nature of the energy utilizing systems associated with cell division and growth.

Thus, in summary, we can say that living systems in reality represent a play of H_2O. Plants, by absorbing sunlight with the aid of chlorophyll molecules, are able to separate water into its elements, hydrogen and oxygen. The oxygen is returned to the atmosphere. In turn CO_2 is absorbed and combines with the hydrogen atoms to form carbohydrates and other essential foodstuffs. In this manner, energy from the sun is stored in chemical bonds. On the other hand, by a series of complicated reactions, animals reverse the process by recombining H and O to form water. This latter process is accompanied by a release of energy. The energy is either dissipated as heat or converted to work by the cell.

The complicated series of reactions involved have been classified into three major types:

A. Energy yielding reactions
   1) Glycolysis
   2) Krebs cycle
   3) Hydrogen transport and the cytochrome system

B. Energy transfer and storage reactions
   1) Oxidative phosphorylation
   2) ATP + Creatine = Creatine Phosphate + ADP

C. Energy utilizing or converting systems

It is possible to use this outline of over-all energy metabolism of the cell to classify various pharmacological agents as to site and mechanism of action. There are three major sites where various pharmacological drugs might act. They can block energy yielding and transfer reactions. We would like to refer to this as nonspecific drug action; for example, iodo acetate and 2,4-dinitropherol block glycolysis and oxidative phosphorylation, respectively. However, these agents not only interfere with the contractile process but prevent growth, nerve transmission, protein synthesis, and modify cell permeability. In other words, all functions are affected about equally. On the other hand, we have drugs which affect specifically only one physiological function; such as specific inhibitors of growth, nerve transmission, etc. This type of action should be referred to as specific drug action. Unfortunately, very little is known of biochemical reactions involved in specific drug action. These biochemical systems are usually referred to by pharmacologists as receptors--a waste basket of ignorance. Experimental investigation in this field is extremely difficult and fraught with many technical problems. If one is to say that a certain biochemical reaction governs a certain physiological function final proof must be obtained from a living functioning system and not from homogenates or tissue brei. This methodology does not appeal to chemists. They search for molecules, determine purity, M.P., rates and specificity of chemical reactions. Therefore, the physiologist and pharmacologist must be ingenious not only in the development of techniques but in hypothesis. As a result of this, hybrids are beginning to appear in

various pharmacology and physiology departments throughout the world such as biophysicists, enzymic pharmacologists, etc. The biophysicist appears to be a successful mutation or cross in that he is willing to attack the problem with the methods of physics and at the same time develop respect for the biological system.

LABORATORY EVALUATION OF DRUGS

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Introduction

"Experiment and you will say what you have seen." Francois Magendie (1)

In times past, discoveries of new drugs were few and far between. Most drugs were naturally occurring substances extracted ready-made from plants, animals, and minerals. Since most substances used in early times either were fairly innocuous and relatively free from toxic effects or were so toxic that their potentially lethal effects were well recognized, laboratory testing before clinical use was a casual procedure, if done at all.

Today, new drugs are introduced at the rate of one a day (2). Most of these are made by chemists who have many and varied methods of synthesis at their disposal. Chemical synthesis of a new drug may be suggested in several ways: chemical analogy with substances having known therapeutic properties; use of chromatography and other sensitive new methods for detecting small quantities of naturally occurring materials with biological activity, and exploration of new families of compounds through new technics of chemical synthesis. In addition, synthetic chemists have created thousands of compounds which bear little resemblance to known therapeutic agents, but some of which may eventually be shown to possess desirable pharmacological properties. Because many man-made drugs are highly selective in their effects and alter body physiology in very discrete ways, and because the routine screening of synthetic chemicals has resulted in the discovery of many therapeutically useful agents, it is not surprising that the laboratory evaluation of drugs has become an important part of pharmacology.

When does the evaluation of a new drug begin? It is possible and even probable that the process of evaluation may begin prior to the chemical preparation of the agent. The modern pharmacologic concept of structure-activity relation leads directly to this possibility. Although still in its infancy and far from perfect, the structure-activity-relation concept is increasingly applied in the deduction of probable pharmacologic activities of compounds before their preparation in the chemical laboratory. The invention of dimercaprol will serve to illustrate this point. Stocken and Thompson (3) observed that vesicant arsenicals exposed to protein combined only with SH groups, and that one molecule of the arsenical combined to form a ring with two SH groups situated close to each other on the same protein molecule. This observation, an extension of the original findings of Voegtlin (4), Rosenthal (5), and Eagle (6), suggested that dithiols should be much more effective arsenic antagonists than were the

monothiols. The validity of this reasoning was established by the subsequent synthesis and laboratory testing of dimercaprol (BAL). Numerous other examples could be presented from other areas of pharmacology. Thus, a tentative prediction of pharmacodynamic or chemotherapeutic potentialities of a nonexistent chemical, at least in some areas of pharmacology, is possible within the limits of present knowledge of structure-activity relation. As promising as this might seem, the state of prediction of clinical usefulness from knowledge of chemistry alone, as pointed out by Toman (7), is so primitive that one cannot envision the millenium when new drugs will go directly from the synthetic organic chemist to the physician without the intervention of the laboratory pharmacologist.

When does the evaluation of a drug end? Evaluation of a particular drug continues as long as the accumulated knowledge concerning it suggests sufficient valid clinical application to justify continued therapeutic use. Indeed, no drug in use today has been completely and finally evaluated, regardless of its antiquity. Thus, one must conclude that drug evaluation is an evolutionary process continually sustained by advances in scientific knowledge.

General Pattern of Drug Evaluation

The crucial position of pharmacology in the critical evaluation of drugs has been graphically outlined by Leake (8), and the Council on Pharmacy and Chemistry (now known as Council on Drugs) of the American Medical Association has published a general pattern for the routine evaluation of drugs (9). Although the latter was designed primarily to aid manufacturers and scientists who undertake the evaluation of new drugs, the technics and objectives are of importance to all pharmacologists because they constitute the very core of pharmacological research on both known and new drugs. Therefore, the plan suggested is reproduced below in outline form.

I. Preliminary Observations

The preliminary experimental observations with a new agent should give the clue to the possible field of usefulness.

II. Definitive Study

The following general types of study should prove to be applicable to most new drugs, keeping in mind that these are suggestive and not necessarily exhaustive.

A. Biochemistry: General properties of the drug, including solubility, stability; studies of absorption, reabsorption, fate, distribution and excretion of the drug; quantitative data on these points where possible; mode of detoxification (excreted unchanged, oxidized, reduced, acetylated?); effect on enzymes, blood and tissues; chemistry of body fluids and tissues; production of toxic products during course of metabolism.

B. Pharmacodynamics: Local--Tests of irritation on skin, eye, alimentary canal; intradermal irritation, sensitivity or anesthesia; tests of protoplasmic depression or toxicity,

and reversibility of effects on cilia, nerve trunks, mucosa; hemolysis, antihemolysis, and blood pigment changes.

C. Experimental Functional Pathology: Effects in experimentally induced pathologic states, e.g., smooth muscle spasm, hypodynamic hearts, fibrillations and arrhythmias, hypertension, respiratory depression, edema, shock, burns, anemias.

D. Chemotherapeutic: Effects in preventing specific experimental infections; effects in combating experimental infections or actions of toxins; antagonists of chemotherapeutic agents, e.g., pus, serum, tissue products; distribution in inflammatory states, e.g., meningitis, dermatitis; minimal effective dosage (ED50).

III. Toxicity

The data obtained from the above studies will serve as a guide in the clinical application of the product and doubtless will also show evidence of undesirable or potentially harmful effects. If such effects are not observed a careful search must be made for them. The outline below sets forth in general terms the scope that these studies should embrace:

A. Acute Toxicity: Dosage response curves in three or more species; objective symptoms; statistical calculations for comparative studies; simultaneous comparative determinations of other substances; variations in toxicity with method of administration.

B. Subacute Toxicity: Large daily doses to one or more species for six to twelve weeks; microscopic pathology.

C. Chronic Toxicity: Three or more species; at least one species for the life of the animal; several dosage levels graduated to produce from no effect up to pronounced lesions, and possible shortening life span; microscopic pathology; effects on voluntary activity, e.g., running or other performance as evidence of more subtle functional changes.

D. Local Effects: Sensitization; skin irritation; mucous membrane irritation; photosensitization.

E. Special Studies: Reproduction; distribution and storage; effect of diet; effect of environment; kidney and liver function tests.

It is obvious that a complete laboratory examination of a new drug, such as outlined above, is time-consuming and costly. However, Leake and associates (10) have questioned whether the experimental background for new drugs should be as detailed as the "pattern" described by the Council, and they suggest it is as important to study the toxic hazards of new drugs in disease states as it is to determine the efficacy of drugs in such states. Therefore, they recommend that primary laboratory experiments should be directed toward an exhaustive study of the toxic hazards and that extensive pharmacodynamic experiments should be secondary. In contrast, a recent report (11) has advocated that drugs which show promise by laboratory screening procedures, but which can only be obtained in relatively small quantities on a research basis, should be tested directly in

man. It is generally agreed that final assessment of the therapeutic value of a new drug must come from studies made directly in human patients, but short cuts are potentially dangerous to the health of the participating subjects, particularly when drugs with novel chemical structures are being tested. In addition, ethical and medico-legal considerations are involved when an abbreviated approach is employed. Nevertheless, these divergent views serve to emphasize the importance of a discussion of the laboratory evaluation of drugs, and suggest that it would be worthwhile to direct attention to some of the factors which limit the predictive value of procedures currently employed.

Drug Screening

The ultimate objective of the routine screening of chemical agents for biological activity is to sort out those drugs which may prove valuable in the prevention or treatment of specific disease entities. The prediction of possible clinical usefulness is based on the ability of the candidate drug to alter, in laboratory animals, the experimentally induced or naturally occurring counterpart of the particular disease entity, or to modify normal tissue or organ function in such a way as to suggest an effect of value in human pathological states. Unfortunately, experimental pharmacology has not yet reached the point where the majority of the principal diseases which occur in man can be reliably simulated in animals. Even the most dependable laboratory tests, such as the analgesic and antiepileptic screening devices, have inherent weaknesses which are occasionally revealed when candidate drugs with novel chemical structures are subjected to clinical trial. The inadequacies of present technics are emphasized by the fact that many of the drugs widely employed in neurology and psychiatry today did not originate as a result of correct predictions from planned laboratory investigations but were "discovered" only after they had been tried clinically for some other reason. Numerous reviews and conference reports (12, 13, 14, 15, and others) have emphasized the need for more reliable screening technics.

What are some of the major obstacles to the routine screening of drugs? Firstly, the etiology of many diseases for which drug treatment is sought is not completely understood. For example, knowledge of the cause of epilepsy is still incomplete, and thus therapy on the basis of etiology is not yet possible. Yet the fact that this disorder is characterized by certain functional disturbances which can be reproduced in animals allows for a fairly rational approach to the symptomatic therapy of this disorder, and drug treatment is directed toward control of the seizures rather than removal of the cause. Thus, useful antiepileptic agents can be detected on the basis of their anticonvulsant properties in animals, despite the fact that the mechanisms of the various forms of experimentally-induced seizures in laboratory animals may have little in common with the causes of epilepsy in man. Therefore, even when the etiology of a particular human disease is unknown, one attempts to induce alterations in laboratory animals which simulate the primary functional disturbance of the disorder, in order to devise a screening test for detecting agents which might prove useful in the symptomatic control of the disease in man.

A second obstacle to a more adequate screening of drugs is that it is difficult to produce the exact counterpart of many human disabilities in laboratory

animals, even when the causes are known. For example, in the field of pain, the comprehensive review by Beecher (13) emphasizes the fact that the reflex response to a noxious stimulus, commonly used in the measurement of experimental pain variously evoked in laboratory animals, is quite different from the pathological pain in man with its associated psychic components. Although some investigators have devised screening technics for analgesics which combine anxiety or fear with experimental pain, it is quite unlikely that this contrived situation approximates the real state which arises when pathological pain or trauma is experienced in man. This very familiar example serves to illustrate the fact that it is rarely possible accurately to duplicate in laboratory animals a particular human syndrome or disease. Hence the experimental pharmacologist is frequently forced to adopt another line of action. He can adopt as a model a drug that is already successful in clinical therapeutics and then attempt to duplicate, in other chemical structures, the profile of pharmacological effects of the model. The objective of this type of screening is not to find a novel therapeutic agent but to find a drug that will be preferable to the model compound, for any of a number of well-known reasons, including safety, potency, duration of action, minimal side effects, patient acceptability, cost, and many other features. It is this approach which prompts many investigators to emphasize the importance of a battery of tests and profiles of action rather than a single procedure. Although such an approach is essential, it is limited in that it is not directed toward the challenging new fields of therapy for which novel drugs are not yet available.

A third obstacle which confronts the pharmacologist in the laboratory evaluation of potential therapeutic agents is the fact that the goals of therapy for many diseases have not been clearly defined. This is particularly true in the case of mental diseases, for example, schizophrenia. Thus, it is difficult to obtain a clear picture of the nature of the psychological effects which the ideal "psychotherapeutic" drug should produce. Even if the pharmacologist's armamentarium included a wide range of tests which could reliably be used to select drugs with various specific psychological effects, it would still be difficult to decide which of these drugs might be beneficial in schizophrenia. Progress in this area might be made, however, by defining the goals of therapy in the same manner as in other fields of experimental therapeutics. Thus, Evarts (16) has suggested that once the primary psychological disorders which characterize schizophrenia are sorted out, therapy can then be directed toward their amelioration. Until the primary functional disturbances in schizophrenia and in other mental diseases have been disclosed with certainty, progress in this area will be slow.

A fourth obstacle is one which imposes restrictions on the amount of information which can be derived from the laboratory evaluation of drugs. This is the tendency of many workers to confine their observations to the effect of a single dose for a particular endpoint. The studies of Barbara Brown (17) on intact animals emphasize the importance of scanning the entire pharmacological dose range, i.e., all those doses which produce the particular observable effect for which the agent is studied. She has shown that dose-depressant profiles for tranquilizers differ in four discrete ways from those of the barbiturates, as follows: the extraordinarily wide dose range producing depressant effects, the absence of a hyperactive phase, the inability to produce complete immobilization,

and the long duration of action of doses causing low levels of activity. These observations on the dose-depressant profiles of sedative-hypnotic agents also serve to illustrate how much can be learned by the careful study of intact animals given the drug over the full dose-effect range.

Since many drugs exhibit their characteristic effects in human patients only after a period of chronic administration, it would appear equally important to screen drugs for pharmacological activity after chronic administration. This suggestion is supported by the fact that some clinically useful agents, for example many vitamins and hormones, exert little useful effect when administered in a single dose, whereas other drugs, for example morphine, become less effective when administered frequently. Therefore, it would appear desirable to study in laboratory animals the pharmacological effects induced by the chronic administration of the drug. Such studies, in addition to revealing valuable information on tachyphylaxis and cumulative potentialities of the drug, might reveal valuable therapeutic agents which otherwise would be missed. Indeed, one wonders how many drugs have escaped detection because of the common practice of screening for pharmacological activity after administration of single doses.

A fifth obstacle is one concerned with the proper laboratory evaluation of drug mixtures. Despite the increased attention currently given drug mixtures by drug manufacturers and clinicians, comparatively few of them have been subjected to laboratory study prior to clinical use. The mixtures and doses employed are selected on the basis of trial and error or on the basis of impressions gained from previous clinical experience with the individual agents. This potentially dangerous procedure is encouraged by the complex nature of the problem and the lack of simple reliable laboratory methods for the evaluation of combined drug effects. For those interested in the theory of drug interactions and the difficulties encountered in the laboratory testing of drug mixtures, the scholarly and authoritative review by Loewe (18) is recommended.

A sixth obstacle is one which limits the predictive value of laboratory screening procedures. There is often a large measure of uncertainty when one attempts to extrapolate to man the results of data obtained in animals. It is generally agreed that, in certain areas, the results obtained in laboratory animals can be used reliably to predict the pharmacological effect in man. Examples of such areas are the effects of drugs on neuromuscular transmission, impulse conduction in nerve, diuresis, blood pressure, etc. The high reliability with which extrapolations between phylogenetic levels can be made in the case of these discrete examples results from the fact that a great deal is known concerning the functional basis of the effects observed; consequently, tests used to identify drugs effective in these areas have become highly selective. On the other hand, extrapolations from animals to man in less clearly defined areas of pharmacology become more difficult. To site an extreme example, extrapolations based on the effects of drugs on more complex functions in laboratory animals, such as behavior, are less reliable than those based on the actions of drugs on an identifiable enzyme system at the cellular level.

No one would deny that there are many obstacles, other than those mentioned, which limit the predictive value of specific laboratory screening tests. Those enumerated represent major general weaknesses of currently employed laboratory

procedures. Therefore, the search for new screening technics which take these obstacles into consideration should be continued.

Definitive Study

The definitive pharmacological study of clinically useful agents is a continuous process and not merely or necessarily a prelude to clinical trial. Certainly the definitive studies outlined by the Council are highly desirable, but far more extensive than can be done on any single drug prior to actual trial in human patients. Indeed, it is doubtful whether the sum total of the knowledge suggested by the Council, desirable as it might be, is actually available for any single therapeutic agent. Nevertheless, it is still important to study basic mechanisms of drug action, and to use drugs as tools to elucidate the physiological and biochemical substrata on which drug actions are based. Such endeavors are currently characteristic of the rapidly growing field of psychopharmacology. Although the "practical man" may sometimes grow impatient with what may appear to be theoretical studies, they open the road, eventually, to the rational development of new therapy.

Toxicity

The acute and chronic toxicity studies as outlined by the Council are, in general, so well known and understood that little comment is necessary. Nevertheless, even these routine studies may give highly variable results. For example, when mice are employed as test animals for certain sympathomimetic amines, Chance (19) has shown that the LD_{50} is 10 times higher for singly confined animals as compared to aggregated mice. This observation, recently confirmed by Lasagna and McCann (20), emphasizes the fact that even rodents are responsive to their social environment and suggests that certain types of acute and chronic toxicity studies should be done both with individually isolated animals and with uniform groups of animals housed together under similar conditions.

The ultimate safety of any drug used in the treatment of disease depends upon the relation between the dose effective against the particular disease and that which evokes some toxic effect. Significant data with regard to the effective dose in human disease must come from clinical trial. On the other hand, the toxicity of the compound should be so well understood from laboratory studies that human life is not sacrificed in preliminary clinical experiments. Ideally, this means that the laboratory profile of toxicity of each drug should be determined prior to clinical trial. This objective, however, has never been fully realized for two reasons. Firstly, available laboratory tests are either not generally reliable or they are incapable of detecting certain types of toxicity. Secondly, several laboratory tests which can demonstrate particular types of toxicity are frequently neglected.

Available laboratory tests in animals are weak or entirely lacking in their ability to reveal the potentiality for causing serious skin disorders and liver and bone marrow disturbances which represent major hypersensitivity reactions to

drugs in man. Species differences contribute to the difficulty encountered in testing for certain toxic effects on the blood. For example, it is well known that methemoglobin is not readily induced in rodents. It is possible but not definitely proved that drug-induced skin rashes, and liver and bone marrow disturbances are hypersensitivity reactions peculiar to man. Regardless of the difficulties involved, it is the task of the pharmacologist to devise, if possible, methods which will reveal such untoward effects and toxic manifestations in laboratory animals so that the profile of toxicity will be known before the drug is used in human beings.

Despite available laboratory tests, several areas of toxicity are frequently overlooked. Examples of neglected areas include fertility and reproduction, and behavioral toxicity. The importance of laboratory studies designed to elucidate the effect of new drugs on fertility and reproduction is shown by reference to the actions of some comparatively new agents. Nitrofuran compounds have been shown to alter reproduction in rats when fed in doses that do not have any other detectable effects. In males, these compounds completely arrest spermatogenesis at the primary spermatocyte stage, whereas in females they interrupt gestation by a direct action on the fetus (21). In view of the number of new drugs introduced and since no concerted effort has been directed toward the routine testing for these pharmacological effects, one naturally wonders if other novel agents now employed clinically, including antimetabolites and antineoplastics, exert adverse effects on the reproductive system.

The widespread and continuous use of the phrenotropic drugs, representing several new classes of agents acting upon the central nervous system, has focused attention upon a different type of potential untoward effect known as "behavioral toxicity." The term behavioral toxicity refers to the deleterious action of such drugs on skilled motor performance, perception, learning, judgment, memory, and similar high-level psychic functions. Fortunately, a few people are deeply concerned with this kind of drug toxicity and are currently striving to devise tests which are capable of detecting such effects in laboratory animals. In the meantime, much can be learned about this little understood potential hazard by the careful clinical study of patients taking these drugs.

There may be other laboratory tests for toxicity with even more obvious weaknesses than those cited above. Likewise, there may be other areas of toxicity which are either neglected or cannot be evaluated by present technics. Nevertheless, the examples mentioned serve to direct attention to some of the shortcomings of currently available toxicity tests and to emphasize the importance of the continued search for new and more reliable laboratory methods for the determination of the toxicity spectrum of candidate drugs.

The preceding examples and discussion may appear to draw a sharp line of demarcation between the laboratory evaluation of new drugs and their first use in human beings. However, any such implied division is quite artificial. Indeed, the preliminary clinical assessment of a new drug is still an experimental procedure and should be carried out as a direct extension of the laboratory evaluation of the drug. The proper integration of these two areas has been admirably discussed by Isbell (22), and one interested in this topic should consult his authoritative contribution.

Summary

Drug evaluation is an evolutionary process continually improved by advances in scientific knowledge. Methods for the laboratory appraisal of drugs must remain flexible and no general pattern of procedure can be recommended. The broad scope of the problem is indicated by the general procedures suggested by the Council on Drugs. Examples are cited which indicate the validity of the use of laboratory screening methods for the detection of new therapeutic agents. However, laboratory tests in general have inherent weaknesses which limit their predictive value. The incomplete understanding of the etiology of many diseases; the difficulty of producing the counterpart of human disease in laboratory animals even when the etiology is understood; the fact that goals of therapy for many diseases have not been defined; the general tendency to screen drugs for pharmacological activity after a single dose rather than after a period of chronic administration; the lack of simple reliable laboratory methods for the evaluation of drug combinations, and the uncertainty with which laboratory data may be extrapolated from animals to man are cited as major obstacles which contribute to the limitations of currently employed procedures. Attention is directed to the fact that studies on the basic mechanisms of drug action and the use of drugs as tools to elucidate the physiological and biochemical substrata on which drug actions are based are essential to the rational development of new laboratory procedures and new therapies. The importance of adequate toxicity studies prior to clinical trial is emphasized. Evidence is presented which indicates that, under certain circumstances, acute and chronic toxicity should be determined in individually isolated animals as well as in aggregated animals. Blood dyscrasias, skin lesions, and liver and bone marrow disturbances are cited as examples of toxic effects which cannot be readily detected at present in laboratory animals. Fertility and reproduction, and behavioral toxicity are cited as representative of areas of toxicity frequently neglected in laboratory studies. It is concluded that future progress in the laboratory evaluation of drugs is dependent upon the pharmacologist's recognition of the weaknesses and limitations of present methods and his continual search for more reliable laboratory procedures.

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THE CLINICAL EVALUATION OF DRUGS

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My task is to discuss the clinical evaluation of drugs, and, of course, the minute we talk about this kind of thing we are confronted with two great problems. There are the drugs which produce objective change, that is, change in hemoglobin content or in urine output, changes that can be physically measured. Then we are confronted by the problems of measuring the effects of drugs which produce subjective change, that is, drugs which produce changes in symptoms, changes which are apparent only to the individual who happens to be experiencing them, those changes which cannot be recorded mechanically. My experience has been largely with this latter group of drugs, those which influence subjective change, and since time is limited, I should like to confine what I have to say about the clinical evaluation of drugs, at least this morning, to this group of agents. I think we should recognize that in recent years the limelight in therapeutics has been stolen, if you will, quite reasonably, quite understandably, by the chemotherapeutic agents. At the same time we must remember that a very great deal of medicine still consists in the treatment of symptoms and I suppose of all symptoms the most urgent in the sense of requiring relief is the symptom of pain. The work that we've done with pain over the last decade and a half is a sort of prototype serving to guide us in the study of other kinds of subjective responses. That working hypothesis has not yet had sufficient test or trial so that we can see just how broad it is, but I do believe that there is a reason for thinking that the types of controls which have been found essential may be more broadly applicable than to problems of pain alone.

I should like to call your attention to the fact that there are several groups of drugs dear, reasonably enough, to the hearts of pharmacologists, which are closely related. There are sedatives, hypnotics, analgesics, ego-depressants and anesthetics. A small dose of a barbiturate is a sedative, a little bigger dose is a hypnotic, still more is an analgesic, still more is what might be called an ego-depressant agent, "truth serum" in the newspapers, and anesthetics. Now when we can go through all five of these classes by the simple expedient of increasing the size of the dose of a given drug, I am inclined to doubt that there are remarkable differences in the basic actions of these agents, but that remains to be shown. The reason I mention these five groups is to indicate that a broad attack on this field has been useful to us because in studying the analgesics we've learned things about anesthetics, etc. There is useful cross-fertilization of ideas from study of the several groups. As everybody in this room doubtless knows, ever since anesthesia came into existence people have tried to explain how it acts and while there is a meager collection of facts which will surely have to be incorporated into any final explanation of how anesthesia can come about, we are still very far removed from being able to understand the nature of the anesthesia process, but in the past it has always been customary to study

full anesthesia. To us it seemed that we might learn something about the nature of the anesthesia process by studying the stages leading up to anesthesia. That's another reason why we've been particularly interested in these four classes of agents which lead up to the anesthetic state.

Well now, just a brief word about our approach. I'm not going to discuss technical matters with you unless you want to, but just a word at the present time about these technical matters because there are other more interesting things to talk about. I should like to say that in the work on pain we work with post-operative wound pain. We work with groups of individuals, generally not fewer than 25 and often more than that. We have set up standards of what we are going to call pain relief, and I can go into those later if you wish. We inspect the subjects 45 to 90 minutes after they've had drugs or placebos administered to them and they must say that pain is half gone at least for satisfactory results. That may seem like rather a childish approach, but that is a judgment patients find easy to reproduce. I suppose it simply means to them the pain has been tremendously lessened. Now this is pathological pain and this afternoon when we talk about some mechanisms, I think it might be well to say a few things about the differences between experimental pain and pathological pain. Dr. Swinyard referred to those in his talk. Well now, what evidence do I have that we're not deceiving ourselves in dealing with agents in this way? Of course, we always use the "double-unknown" technique, we have placebos that serve as unknowns, we use correlated or cross-over data, all subjects get all drugs, we use a mathematician to help us demonstrate valid differences between the agents studied. We've administered these things in random order.

Having done all that, how do we know that we're getting anything like a dependable quantitative data? How can I draw conclusions from post-operative wound pain? Well, that's a perfectly fair question so I have some data which indicates that pain derived in other ways gives comparable results. Dr. Houde of the Sloan-Kettering Laboratory at the Memorial Hospital in New York provides a good check. We found, using a comparable number of patients in a comparable period here that morphine would relieve satisfactorily in one group 66 per cent of the patients, in another group 69 per cent, whereas Houde found that 65 per cent were relieved by 10 mg. of morphine. His patients have pain arising from metastatic disease, our patients have pain arising from post-operative wounds. In other words, these are very different scurces of pain and yet the data check remarkably. Dr. Houde was using our techniques at the time and we are very glad that he did. We found that a placebo relieved 39 per cent of individuals in that group, and Houde found 42 per cent. I think one must say that these checks are quite good.

I can indicate to you a little more "scholarly" approach to these matters. We had an outside individual make up for us two series of solutions. There are six flashes in each series. We found when we had got through the work that both series of flashes contained morphine. One series had always 10 mg. of morphine per cc and the other series of flashes had different doses of morphine, 2, 4, 6, 8, 10 mg. per cc. Now graphs were made and where the two lines cross there is equivalence of action. We found when we got through that we had equilibrated 10 mg. of morphine to 10.8 of morphine and 7 per cent error. Of course, it is not quite as simple as that (in an audience this size there is always at least

one statistician if not more). These are not lines that cross, they are bands that cross. So it is sounder if one calculates out the regression lines and this adds another 2 per cent. So with controls of the kind that I mentioned, we can get data here which are accurate within a 10 per cent error. The point I'd wish to emphasize here is that if one sets up the controls properly he can measure subjective responses and effects of drugs thereon as accurately as one ordinarily measures objective findings. I submit that one can't count red cells much more accurately than within 10 per cent error, nor can one measure blood pressure more accurately than within 10 per cent error under most circumstances. And so I think we need not be defeatist about the difficulties of measuring these things, if we will but set up the controls as we should. So much then for reasons for confidence.

I could show you a dose effectiveness curve and from this I could show you the action of a 7 1/2 mg. dose is almost as effective in pain-relieving power as twice as big a dose. There is a tendency for dose-effectiveness curves to form a plateau. There is a ceiling effect here and I think all of us in the past have probably been guilty of believing that if a little was good, a lot more was better so that we've overemphasized the effects of increasing dosage. In some more recent data where we have compared much more severe pain than this involved in the foregoing remarks, we find that 10 mg. will relieve 66 per cent of our patients and 15 mg. will relieve 77 per cent of individuals. Now that is barely statistically significant at the 5 per cent level. It took a large series of cases to indicate there was a real difference here. We can get somewhat more pain relief by 50 per cent increase in drug dosage. We do so at the cost of rather severe increase in side effects. I know that the practical way of expressing potency is in terms of the effect per mg. of drug, but I should like to emphasize here that when we're dealing with subjective responses it's not quite satisfactory to limit our designation of potency to terms of effect per mg. as far as the primary effect goes. Actually when we're dealing with a pain-relieving agent, we're obliged to deal with two scales of values. It's important to know what the pain-relieving power of a drug is, but one cannot separate himself from the necessity to know also what the side effects are. And so, what we have to deal with here is what I like to call the optimal dose. In our experience, the optimal dose of morphine is 10 mg. per dose of morphine. That does not mean that 15 mg. won't give more effect or somewhat more effect, but does give a tremendous increase in side effects.

I should like to indicate to you why it's not satisfactory to deal with potency per mg. of dose alone. Take for example, meperidine or "Demerol," an agent which is widely used. We use 50 mg. of "Demerol," not the 75, not the 100 mg. dose which is used in most clinics; the 50 mg. dose is equivalent to 10 mg. of morphine. If we are to use the classical designation of analgeisc effect per mg. as a statement of potency, we would say that meperidine was a very weak agent, one-fifth as strong as morphine. That's true if one limits his comments to this mechanical approach, but it's dead wrong because meperidine is analgesically equal with morphine. It is certainly equal in terms of pain relief which can be obtained with the optimal dose and in terms of the concomitant side effects, it is as good as morphine.

While mentioning the meperidine I would like to say one more thing about it which has distressed me a good deal. Meperidine was introduced some years

ago and it was pushed on the basis of what we now believe to be three errors, three serious errors. If an individual is sensitive to morphine, of course it's all right to use it, to try it; but to push the meperidine on the basis that it is not an addicting agent is dead wrong. The U. S. Public Health Service Hospital at Lexington contains doctors and nurses who became addicts believing that meperidine was also pushed in the beginning on the basis that it did not depress the respiration, but now we know that it is as depressing to the respiration as morphine is. The third item on which this agent was pushed was that it was said to be a spasmolytic agent. The reverse is true as far as the sphincter of Oddi goes. Meperidine is a spasmogenic agent, if there is such a word, on some smooth muscle. I don't say that these were dishonest mistakes--I don't believe they were at all--but I mention this by way of caution in jumping to conclusions. As was pointed out earlier it's difficult to know what the toxic effect of agents may be and it takes time to find out in man. I think it was ten years before anybody knew that codeine was an addicting agent. These toxic effects sometimes take a long time to show up clearly. It's evident, then, that when we speak of these agents we have to bear in mind not only the primary effects but also their secondary effects as well.

Let's talk a little about the side effects of these agents. What are the things that we have to take into account? We must realize that there are many unsolved problems here. I would like to be able to study analgesic agents in sick individuals because I think it's likely that the incidence of nausea, for example, is less in a man who is in pain than it is in a normal individual, but how to get at it? Symptoms of sick individuals are often like the toxic effects of drugs, so we've been thrown back to the use of normal volunteers for the appraisal of side effects. We've tried valiantly for many years to get at side effects in ward patients and we've had to admit we've failed.

Morphine does depress the respiration. I think the best way to study that is to study the respiration under the stress of breathing 5 per cent carbon dioxide following the work of Loeschke and others.

As for nausea, with a 10 mg. dose (this is a small pilot study typical of many such studies and these are representative figures)four out of ten subjects were severely nauseated by 10 mg. and six out of ten by 15 mg. In another group of fifteen subjects, one was nauseated by a placebo, one by pentobarbital, six out of the fifteen by morphine (this is a 10 mg. dose).

So much for the ordinary kinds of side effects. I'd like now to turn to a different kind of side effect and that is the mental effects of these agents. I should like to tell you about them.

Let's look at these differences in responses to morphine as far as euphoria goes. For example, every textbook I've looked at describes morphine as a euphoria producer and in the most glowing terms and not only morphine but heroin and other narcotic agents as well. The facts I think do not support that statement. In our pilot study (these are representative data; we have many more such observations now), only two out of twenty subjects found morphine pleasant, euphoria-producing by a very careful definition of that term.

Q. Was this a blind study?

A. Oh, yes, all these things are. Of the twenty 80 per cent found morphine dysphoria-producing; 10 per cent were neutral. In normal individuals, that is, but with post-drug addicts at Lexington where we've had the privilege of working, thanks to Dr. Isbell and Dr. Wikler, we found in 30 subjects, 30 post-addicts, that 67 per cent found the morphine pleasant and 13 per cent found it unpleasant. Well, this latter group appears to be the basis for the statement in the pharmacology texts. I don't know if they're quoting De Quincy who lies in the churchyard in Edinburgh or just what the pharmacologists are talking about when they describe these things, but I suspect they are talking about the effects of narcotic agents in post-drug addicts. That's not quite fair. If I were to tell you that a 15 mg. dose of morphine was often fatal, you'd think I was crazy. If I happened to be talking about myxedema patients it might be true. One must specify what he's talking about here and I'm afraid some pharmacologists in writing the sections on narcotics in their books have talked about effects in post-drug addicts rather than effects in normal individuals.

Now there are other ways of getting at these mental effects. We've recently completed a study where we've even been able to get at, to quantify, the mental clouding which comes with the action of these agents. There isn't time to discuss this in detail but I should like to show you just a little of how we've approached this kind of thing. We used volunteer data, we used an adjective check list, one particularly designed in Professor Wendt's department at Rochester, then we also used a kind of questionnaire which we devised ourselves. We contrast various mood changes. For example, we'll take sad and then happy on a 7-point scale: -3, 2, -1, 0, +1, +2, +3. If the subject checks off +3, he's very happy, or minus three, very sad. Now when one contrasts enough comparisons of that kind he surely can get quite a good idea of any changes that may have occurred in his subject according to the way this boundary moves with the passage of time after the administration of the drug. Well, that's one approach.

If one graphs such data one can see that it is possible to get quite distinct differences in mood. One can contrast morphine with the placebo and get rather marked changes with the passage of time, contrasting the feeling of sleepiness with that of wakefulness, or contrasting the dreamy with the not-dreamy state, etc.

We applied this technique to dihydrocodeine, an old agent (apparently its analgesic power had been overlooked though not completely; it has been used in Europe for years as an antitussive agent). We found this agent to have a lot of analgesic power, probably less than morphine though of that order. But it didn't have any side effects in optimal dose, 30 mg. It did not depress the respiration and it did not produce confusion. It did not produce nausea. As a matter of fact if we compared dihydrocodeine with a placebo we found no significant differences at all in thirty subjects. Here's a useful analgesic which as far as we could tell was like a placebo.

When we compared morphine we found significant differences between morphine and a placebo, of course, and in dihydroisocodeine also significant differences After four hours we found that the differences between dihydroisocodeine and the placebo had gradually disappeared because the action of the drug had largely disappeared. Even after four hours there are still large differences between

morphine and a placebo, whereas this new agent, dihydrocodeine, and the placebo remain much the same as far as things of this kind go.

Using techniques of this kind, one can get from them in the clinic certain subtleties of drug action which I think are promising for the future. We've gone on with work of this kind and as I say, now can express quite precisely in mathematical terms, thanks to Dr. Mosteller (he's the statistician who's guided us for years), these changes occurring in response to drug action.

Now in summary I would like to say that the essentials, as far as I'm concerned, for work in this field are the following details of technique. One must work with "double unknowns," unknown to subject and to observer, placebos must be inserted as unknowns; there must be randomization of administration of these agents. One must have a clearly defined standard of what is relief or change. One must use cross-over data or correlated data whenever possible; that is, all subjects get all drugs. If that's not possible, then one must greatly increase the amount of material. One must have mathematical validation of supposed differences. Certainly statistics are no substitute for common sense, but I should like to insist that common sense cannot be preserved sometimes in the absence of a statistical approach.

THE DESIGN OF EXPERIMENTS

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Introduction

The wise and rational use of a pharmacological tool, like that of a drug, is possible only on the basis of experience and familiarity. The tool of statistics, together with its subdivision, experimental design, is no exception, but it does present a somewhat unique problem. Before using a new drug, one usually awaits the results of clinical trials by others in whom one has confidence. However, in the case of statistics, since its value is already established and its use is a professional necessity, some investigators employ it in their experimentation even though they lack the experience and familiarity which they would otherwise consider mandatory.

As a result, it is not surprising that such individuals, and this includes most of us, come under constant criticism by the professional statisticians. Their most frequent criticism is that our grasp of statistics is so superficial that we apply the technics known to us in "cookbook" fashion, indiscriminately both to biased as well as to acceptable data. Bias, they tell us, is introduced most frequently by our neglect of the established formulas for determining the temporal sequence in which treatments are to be performed, and by our neglect of various rules which Finney (1955) suggests might be referred to as the "classical" theory of experimental design. As Mainland (1954) has expressed it, ". . . what most medical research workers need is not, primarily, more knowledge of statistical tests, but a realization of what modern biological statistics implies throughout the conduct of any type of medical investigation." Such criticism has produced both desirable and undesirable results. To our credit, an increasingly greater number of us are discovering the advantages of technics such as analysis of variance. More important, we are learning to design our experiments in a manner which permits these more complex technics to be applied with validity. On the other hand, in the preoccupation to correct our more flagrant errors, we are unmistakably fathering a greater and greater percentage of experiments, which, elegant as they may be statistically, leave much to be desired in terms of their general contribution to solution of the biological problem under investigation. The purpose of this paper is to discuss several of the common errors in the general design of experiments.

Under the intriguing title, "Statistics, sophistication, sophistry and sacred cows," and with appropriate apologies to Russell Lynes, Dr. Louis Lasagna (1955) of Johns Hopkins University recently classified us as various types of "Statistical Snobs." One of the two main varieties is the "Statistical Hayseed" or "Professional Illiterate," the sceptic and disbeliever who is readily recognized by his words. His verbal pronouncements, "You can prove anything with

statistics," and "Nothing has ever been proved with statistics," are alternated to fit the occasion. His characteristic written phrase, "The results are promising and warrant further investigation," is usually affixed to the end of a manuscript in which uncontrolled, inconclusive observations, or more properly, impressions, have been summarized. The second main variety of "Statistical Snob" described by Dr. Lasagna is the "Chi-Square Cavalier" or "t-Test Terror," the crusader for statistics who is recognized by his errors of enthusiasm. One common error of the "Chi-Square Cavalier" is that of "Microstatistical Mirage," emphasis of a statistically significant difference which has little, if any, biological significance.[1] Dr. Lasagna's original paper is recommended to those interested in "Tunnel Vision, Placebo Pushing," and other errors of the "Chi-Square Cavalier," which cannot be reviewed here because of limitations of space.

A special reason for digressing here to call attention to Dr. Lasagna's classification is that "Chi-Square Cavaliers" can also be recognized by their errors in the design of experiments. With appropriate apologies to Dr. Lasagna, I would like to add new subtypes of "Chi-Square Cavaliers" to his original list. I have named these new subtypes the Data Devoté, the Single-Shot Sharpshooter, the Obsessive Regressive, the Quantal Querist, the ED50 Evangelist, and the Tempestuous Timer, and the errors committed by these characters will be discussed in the following paragraphs.

The Data Devoté

In its broadest sense, design of the experiment includes the entire logical structure of the experiment (Fisher, 1951) and begins properly with the formulation of the questions to be answered by the experiment. Since an experiment can answer without bias only those questions posed at the time the experiment is being designed, this initial stage of the experiment is the most crucial. Unfortunately, none is so frequently neglected!

One question asked of an experiment which almost always leads to an inefficient experiment is, "I wonder what drug X will do?" When it is not known whether drug X possesses the stated activity, this simple question is unavoidable. However, once it has been established that drug X does produce the stated effect, new questions must be formulated. For example, if it is thought desirable to compare drug X with several others which produce the same effect, concise questions which express these interests must be phrased, and the experiment must be designed accordingly. Only biased answers can be expected if questions are not formulated until after the data have been accumulated.

Data Devotés, or Numbers Operators, those of us who are more interested in amassing data than in answering specific questions, must ultimately choose between two alternatives, neither of which is satisfactory. The statistically acceptable alternative is to use the data initially collected without benefit of

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[1]An equally succinct expression for this error of the Chi-Square Cavalier is that of Dr. Alfred Gilman of the Albert Einstein College of Medicine: "The benefits of the treatment were more apparent to the statistician than to the patient."

the formulation of specific questions merely to guide the design of subsequent experiments in which the proper questions are phrased at the beginning. As Dr. James Toman, a former colleague now at the Chicago Medical College, has expressed it, data collecting, like stamp collecting, can become an expensive hobby, and most of us cannot afford it. However, the real danger of the Data Devoté lies not in his inefficiency and waste, if he chooses the first alternative, but rather in the possibility that he will yield to the other alternative, namely, to salvage his data and thereby supply the rest of us with biased answers via his publications.

No method has yet been devised for adequately coping with the Data Devoté. Since his errors are not easily detected, reform is necessarily voluntary and occurs only with time and the slow process of enlightenment. That the design of an experiment requires more than the random tossing together of several variables is also illustrated by other examples which follow.

The Single-Shot Sharpshooter

A brochure recently circulated by a pharmaceutical company proudly emphasized that a single large dose of its new sulfonamide congener caused the death of 60 per cent of a group of mice, while the same dose of sulfadiazine killed 100 per cent of a smiliar group of animals. Even if it is assumed that the number of animals included in the comparison was sufficiently large to assure statistical significance for this difference, this typical statement of the Single-Shot Sharpshooter is essentially without value.

It is generally assumed that dose-effect curves for drugs producing the same effect are regular hyperbolic or sigmoid curves which reach the same maximum and which have the same slope along their linear central portions when appropriate transformations have been employed. That dose-effect curves are not necessarily uniform is illustrated by comparison of the effects of phenacemide and diphenylhydantoin on threshold for low-frequency electroshock seizures in mice. In Figure 1, seizure threshold ratios (threshold for the experimental group/threshold for the control group) are plotted as a function of dose of the drugs.[2] If Single-Shot Sharpshooting were to be practiced for comparison of the relative effectiveness of these two anti-epileptic agents, any one of several possible conclusions would be reached, depending upon the dosage level selected for the comparison. Both drugs would be found to be inactive if the comparison were attempted at doses smaller than dose A, whereas diphenylhydantoin would be considered more effective than, or as effective as, or less effective than phenacemide if the comparison were attempted at dose B, C, or D, respectively. Obviously, the true relationship between these two anticonvulsant drugs is revealed only by analysis of the full dose-effect relationship.

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[2]Unpublished observations of the author and Dr. Donald G. McQuarrie, now of the University of Minnesota Hospitals.

Single-Shot Sharpshooting is usually defended by the argument that it is practiced only when additional information about the relative effects of the two drugs is already known. In the clinic where the doses chosen for comparison are equieffective for the desired clinical effect and the sharpshooting is performed to estimate the relative incidence of side effects at this dosage level, the argument does have some validity. However, even under these circumstances, Single-Shot Sharpshooting may be misleading if the slopes of the dose-effect curves for the two effects being compared are not parallel, or if the maximum intensities of the two effects are reached at different dosage levels.

To return to the example of the new sulfonamide congener, even if it is assumed that the log dose-effect curves for the new agent and for sulfadiazine do not intersect, the comparison is still of little value, because it does not furnish precise information about the relative toxicity of the two drugs in terms of dose. The erroneous implication is that "twice the effect" is the same as "twice as potent." One need spend only a few minutes drawing the family of log dose-probit curves to demonstrate that sulfadiazine might be as little as 1.5 times or as much as 10 times as toxic as the new congener.

In summary, Single-Shot Sharpshooting may be misleading because it fails to provide for the possibility that dose-effect curves need not be parallel and need not exhibit the same maximum intensity of effect. In addition, only by coincidence is it ever possible to estimate the relative potency of two drugs by comparing the effects produced by a single dose of each agent.

The Obsessive Regressive[3]

After one becomes convinced that Single-Shot Sharpshooting can be a misleading type of experimental design, he usually adds regression analysis to his statistical armamentarium. Early in his introduction to this useful statistical technic, he learns that straight lines are mathematically advantageous and that the use of certain dose and/or effect metameters almost always yield the desired linearity. Unfortunately, many of us become too preoccupied with demonstrating regression and with performing the validity tests for deviation from linearity and for deviation from parallelism. A potential trap for Obsessive Regressives, those who have developed an excessive fascination for regression analysis, is illustrated in Figure 2. The left-hand panel of the figure illustrates two theoretical <u>log dose</u>-effect lines which exhibit slight deviation from parallelism. If random variation calculated by the usual procedures is sufficiently large to permit the two regression lines to be forced into parallelism, the implication of the slight deviation from parallelism is likely to go unheeded. In contrast, if the data had also been examined as a <u>dose</u>-effect relationship, as in the right-hand panel of the figure, the possible difference between maximum intensities of effect of the two compounds becomes sufficiently impressive to prevent its being ignored in future experiments.

Although emphasis upon achieving linearity for regression analysis may obscure clues to possible differences between drugs being compared, not all

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[3]The author wishes to express his thanks to Dr. Walter S. Loewe for his suggestion of this title.

potential traps for the Obsessive Regressive are so readily detected. The example in Figure 2 was not selected to support a plea that all data be subjected to graphic analysis by several different methods. Rather, the example was chosen to emphasize that regression analysis, useful as it is, reveals information about the drugs being compared only over the range of doses included in the analysis. One can avoid earning the dubious title of the Obsessive Regressive by remaining aware of this limitation of the method. It makes little difference what devices we employ to remain cognizant of the possibility that important differences between drugs may exist outside the dosage range studied. Recommended devices include constant alertness, full appreciation of the distortions produced by selection of the usual log dose-effect and log dose-probit transformations, and use of aids such as multiple graphic analysis.

The Quantal Querist

The effect of a drug can be expressed either by the intensity of a measured effect or by the percentage of a population sample which exhibits a carefully defined quantal endpoint. Most of us appreciate that any measured effect can be readily converted to a quantal endpoint, and such conversion is frequently practiced to simplify collection of the experimental observations. Most of us also recognize that such conversion to be practical must make collection of the data at least twice as simple, since approximately twice as many observations are required in a quantal procedure as in a quantitative comparison to achieve the same degree of precision (Gaddum, 1953). Consequently, selection of the quantal endpoint rather than the measured effect, whenever the choice is possible, must not be a routine conversion, but rather one in which ease of collection of the data, ease of calculation, degree of precision required, and similar factors are considered and weighted appropriately.

In addition to being influenced by various practical considerations, the choice between a quantal endpoint and a measured effect must also be based upon knowledge of the full dose-effect relationship between the variables under investigation. Potential traps for Quantal Querists who blindly select the quantal procedure are illustrated in Figures 3 and 4. In Figure 3, the dose-effect curves for phenacemide and diphenylhydantoin for elevation of low-frequency electroshock seizure threshold in mice are again compared. Consideration of these curves illustrates that, if a quantal procedure for detecting changes in threshold were designed such that the animals were challenged with a stimulus two to three times the average threshold for nonmedicated animals (the level indicated by the lower horizontal dotted line), equieffective doses of the two drugs for low-intensity effect would be estimated with accuracy. However, this quantal procedure would fail to detect the fact that the ability of diphenylhydantoin to elevate seizure threshold is limited. On the other hand, if a quantal procedure were designed such that the animals were challenged with a stimulus equal to ten times the average threshold for nonmedicated animals (the level indicated by the upper horizontal dotted line), activity of phenacemide would be detected but diphenylhydantoin would be rated as inactive. Thus, in practice, the Quantal Querist is little more than a "horizontal" Single-Shot Sharpshooter in disguise.

After something is known of the relative effects of representative agents, an experimenter may decide that he can afford to sacrifice information in

exchange for practical advantages that the quantal procedure may offer. Such decision labels the experimenter a Quantal Querist only if he makes his choice blindly and only if he fails to remember that he is sacrificing information in the process. However, when the loss of precision inherent in the quantal procedure is taken into consideration, exploration of the full dose-effect relationship is just about as economical as performing the quantal comparison, unless the measured effect is much more difficult to evaluate than the quantal endpoint.

As long as the Quantal Querist is armed with only one quantal procedure, he exposes himself only to the dangers discussed in the preceding paragraphs. However, sooner or later, he usually acquires several quantal procedures and becomes vulnerable to the additional trap illustrated in Figure 4. This example has also been selected to illustrate an alternative form of the quantal procedure in which use is made of a so-called "uniformly effective" stimulus. The two solid lines in the figure represent theoretical log dose-probit curves for two stimuli which evoke the same quantal endpoint. For convenience, they may be considered to be drugs which evoke convulsions. In this example the Quantal Querist would designate doses 16 X and 64 X, respectively, as "uniformly effective" doses for the two convulsant drugs. Consider now the consequences of pretreatment of the animals with an anticonvulsant drug which reduces sensitivity of each animal by a factor of two to <u>both</u> stimuli in a <u>nonselective</u> manner. Since the log dose-probit curves would be shifted to the positions indicated by the dotted lines, challenging groups of pretreated animals with the "uniformly effective" doses of the two convulsant agents would evoke the quantal endpoints in 50 per cent and 97.5 per cent, respectively, of the two groups. As a result of the difference in the slopes of the log dose-probit lines, the Quantal Querist is likely to arrive at the erroneous conclusion that the treatment with the anticonvulsant drug has <u>selectively</u> modified the activity of the drug which is characterized by the steeper log dose-probit curve.

Defenders of the Quantal Querists will rally to explain that this potential trap is readily avoided by careful examination of the original log dose-probit curves and/or by repeating the challenge in the medicated animals with greater increments of the "uniformly effective" stimuli. Unfortunately, most Quantal Querists are not so careful; those who are would be well advised to expend equal time and effort on other than the quantal procedure.[4]

The ED50 Evangelist

In part because some quantal endpoints are not readily converted to measured effects, but probably primarily because of the lure of the simplified methods of graphic analysis, most pharmacologists have mastered technics for the calculation of ED50's. Unfortunately, not all have also mastered full appreciation of the limitations of these calculations, and many tend to develop the mistaken belief that ED50's possess inherent stability with time.

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[4]Other defenders of the Quantal Querists will hasten to point out that the arguments of the author are based upon assumptions with regard to the slopes of the original log dose-probit curves and to the parallel shift of these curves by the treatment. These assumptions are acknowledged with the reminder that defenders of the Quantal Querists must also make assumptions to demonstrate that the trap is nonexistent.

The data tabulated in the left-hand panel of Figure 5 are typical of those by which "ED50 Evangelists" justify their erroneous impression that ED50's are stable. In this figure, two series of ED50's for modification of maximal electroshock seizure pattern, as reported in the literature in different years from the same laboratory, are compared. The horizontal dotted lines indicate the 95 per cent fiducial limits for the initial observation of each series. The ED50's for phenobarbital sodium in mice determined in 1954 and in 1956 agree quite satisfactorily with that initially reported in 1953. Since most of us could abstract similar data from our own publications, it is not surprising that some are tempted to join the ranks of the ED50 Evangelists. However, most of us could also accumulate other data similar to those tabulated in the right-hand panel of the Figure. The ED50's for diphenylhydantoin in rats in this series differ by a factor of as much as 4 to 5. Thus, ED50's are not necessarily constant, even in a single laboratory.

In his classical paper in which he proposed the use of the expression "median effective dose," Trevan (1927) cautioned that ED50's do not necessarily possess inherent stability, and Finney, in his standard text on probit analysis (1952), has discussed this topic at considerable length. Both of these discussions have apparently been overlooked by the ED50 Evangelists.[5] As expressed by Finney, standard errors, fiducial limits, or other measures of precision must not be accepted as an indication of the variation to be encountered in <u>any</u> repetition of an experiment. Rather, measures of precision calculated from internal evidence of one experiment relate only to repetition under <u>identical</u> conditions. If an experimenter desires to compare two ED50's and to estimate the precision of this comparison by the usual calculations, the ED50's used for the comparison must have been determined simultaneously. When ED50's determined other than simultaneously are compared, no estimate of the precision of the comparison is possible.

The Tempestuous Timer

In most experiments, the effect of a drug is measured at a single time interval after its administration, usually at a time which is believed to be the time of peak effect. In other experiments, serial measurements of effect are repeated in temporal sequence to permit analysis of the so-called effect-time curve. Proper interpretation of the effect-time curve permits estimation of the effect of the drug at the true time of peak effect and, in addition, provides useful estimates of latency of effect and duration of effect. However, effect-time curves are readily subjected to misleading transformations by the Tempestuous Timer.

One distortion of the effect-time curve frequently performed by the Tempestuous Timer is that in which the effect of the drug is expressed in terms of the area enclosed under the effect-time curve. This combination of intensity of effect and duration of effect into a single expression of the activity of the

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[5]An additional reason for suspecting that Trevan's paper has not been widely read, at least on this side of the Atlantic, is that the symbol for median effective dose proposed by Trevan, ED50, has been altered by most of us to ED_{50}.

drug is sometimes advantageous in analytical (dilution) assays, but it should be avoided in comparative assays and for most other purposes because of the bias which is unavoidably introduced. Consider, for example, the laboratory evaluation of two drugs which produce the same effect but which differ significantly in duration of effect. Let us assume that relative potency of the two drugs for the desired effect has been estimated by a procedure which confounds intensity of effect and duration of effect, while relative toxicity of the two agents has been estimated by the more conventional procedure based only upon intensity of effect. When these two drugs are subsequently compared for relative safety, the comparison will be biased in favor of the drug with the longer duration of effect, since its longer duration will have led to overestimation of its potency for the desired effect but will not have influenced the estimation of its toxicity.[6]

Defenders of the Tempestuous Timer will argue that intensity of effect is unavoidably influenced by factors of absorption, distribution, fate, and excretion, whenever the effect of the drug is related to the dose administered. This argument is correct, but it does not justify the further amalgamation of intensity effect and duration of effect as performed by the Tempestuous Timer. Rather, it should serve to emphasize that special precautions may be necessary in some experiments to minimize or to eliminate the interdependence of these characteristics of drug action. For example, the experimenter interested in demonstrating true potentiation of drug action must be particularly careful to eliminate the influences of absorption, distribution, fate and excretion, and for this purpose, he may have to resort to analysis of the effects of the drugs in relation to their concentrations at the site of action.

Summary

The errors of experimental design discussed in the preceding paragraphs may be classified into two general categories. Experiments designed by the Data Devoté, the ED50 Evangelist, and the Tempestuous Timer are faulty because of the introduction of bias, while those designed by the Single-Shot Sharpshooter, the Obsessive Regressive, and the Quantal Querist may be criticized because they are incomplete. However, in the final analysis, all errors of experimental design can be attributed to a single basic flaw, namely, failure to relate the experiment to the biological problem in its entirety.

While no simple, all-inclusive formula for the proper design of all experiments is possible, it can be stated that the time devoted to the thorough and critical appraisal of a proposed experiment is always a wise investment. In some cases, the dividend may be a refund of time made possible by redesign of a more efficient experiment to yield the same answers. In other cases, the dividend may be the discarding in advance of a proposed experiment that could not possibly supply the desired answers, or it may be the avoidance of an experiment which would later have to be repeated in expanded form in order to supply the

[6]Although it is not the intent of this paper to dwell on mathematical technics, attention is called to the fact that probit analysis, although little used for this purpose, is well suited for estimation and comparison of maximum intensities of effect (Finney, 1952).

desired answers in full. Whatever the dividend, the properly designed experiment usually reflects the fact that the experimenter devoted sufficient time to the initial appraisal to assure that he had acquired visualization of the full shape of the problem.

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POTENTIAL TRAP for the SINGLE-SHOT SHARPSHOOTER

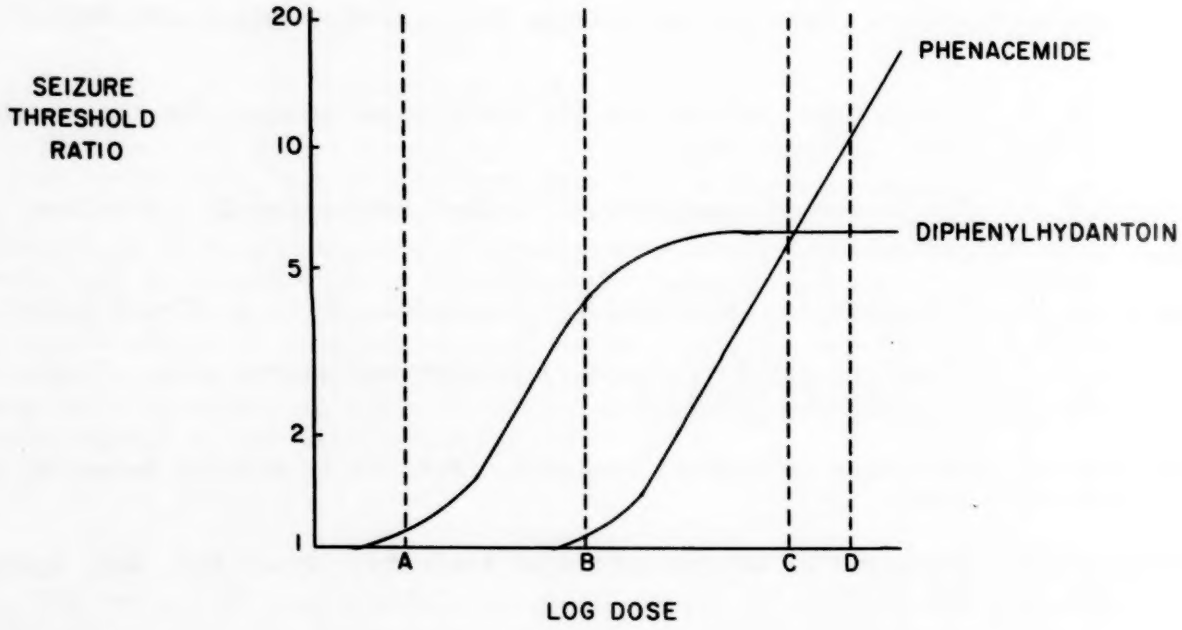

Figure 1. Comparison of the effects of phenacemide and diphenylhydantoin on threshold for low-frequency electroshock seizures in mice, to illustrate a potential trap for the Single-Shot Sharpshooter. See text for discussion.

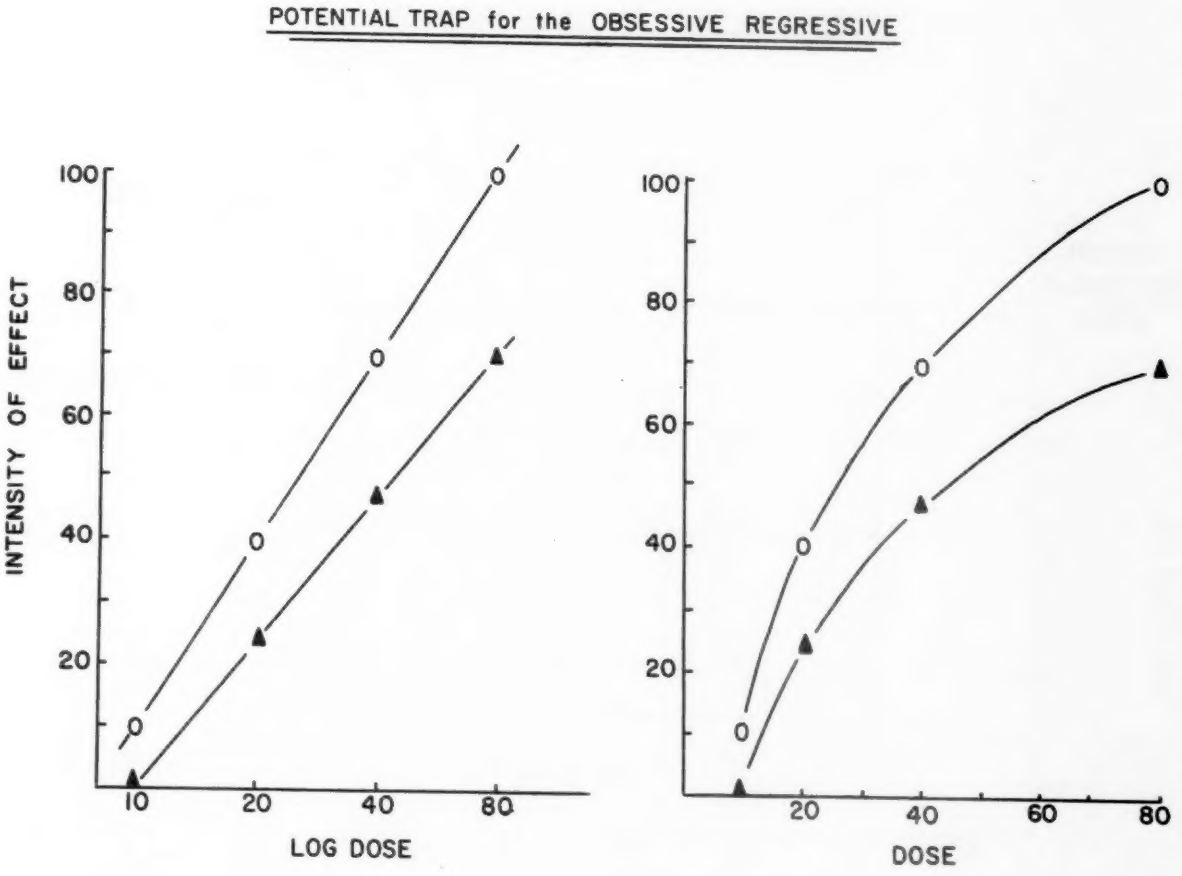

Figure 2. Multiple graphic analysis of two theoretical dose-effect curves, to illustrate a potential trap for the Obsessive Regressive. See text for discussion.

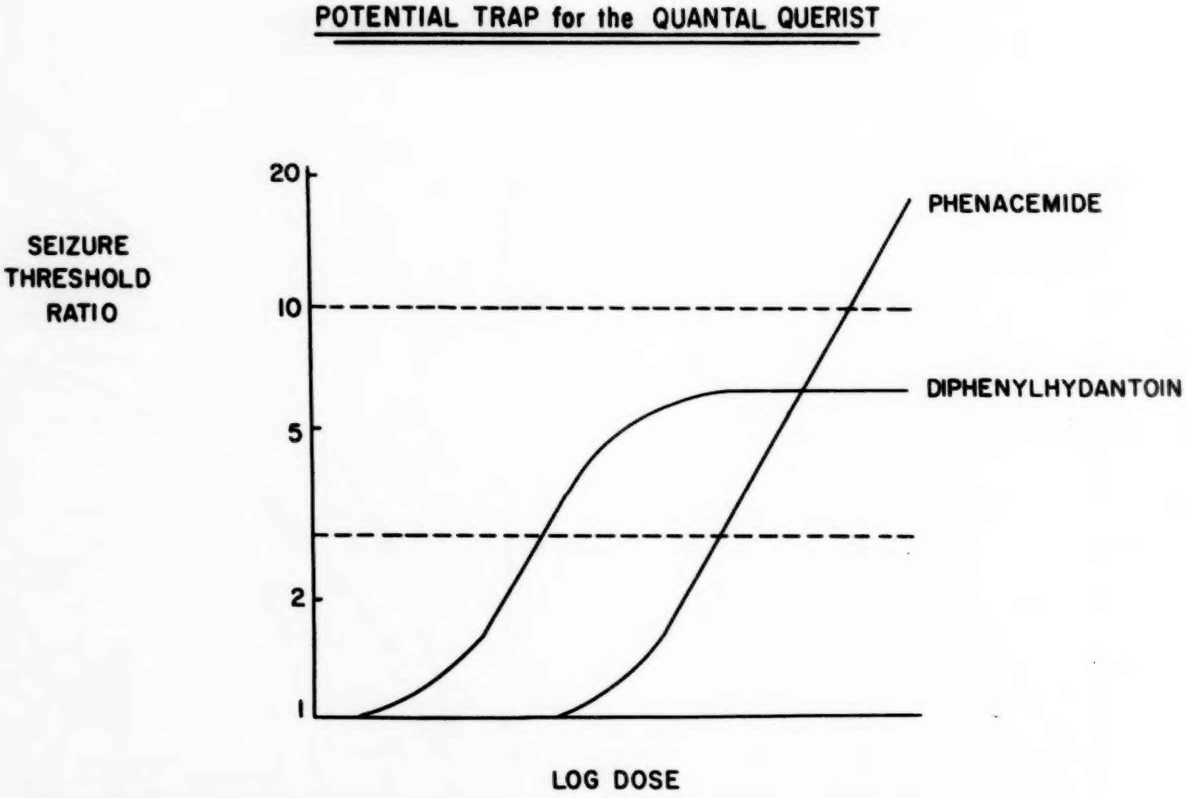

Figure 3. Comparison of the effects of phenacemide and diphenylhydantoin on threshold for low-frequency electroshock seizures in mice, to illustrate a potential trap for the Quantal Querist. See text for discussion.

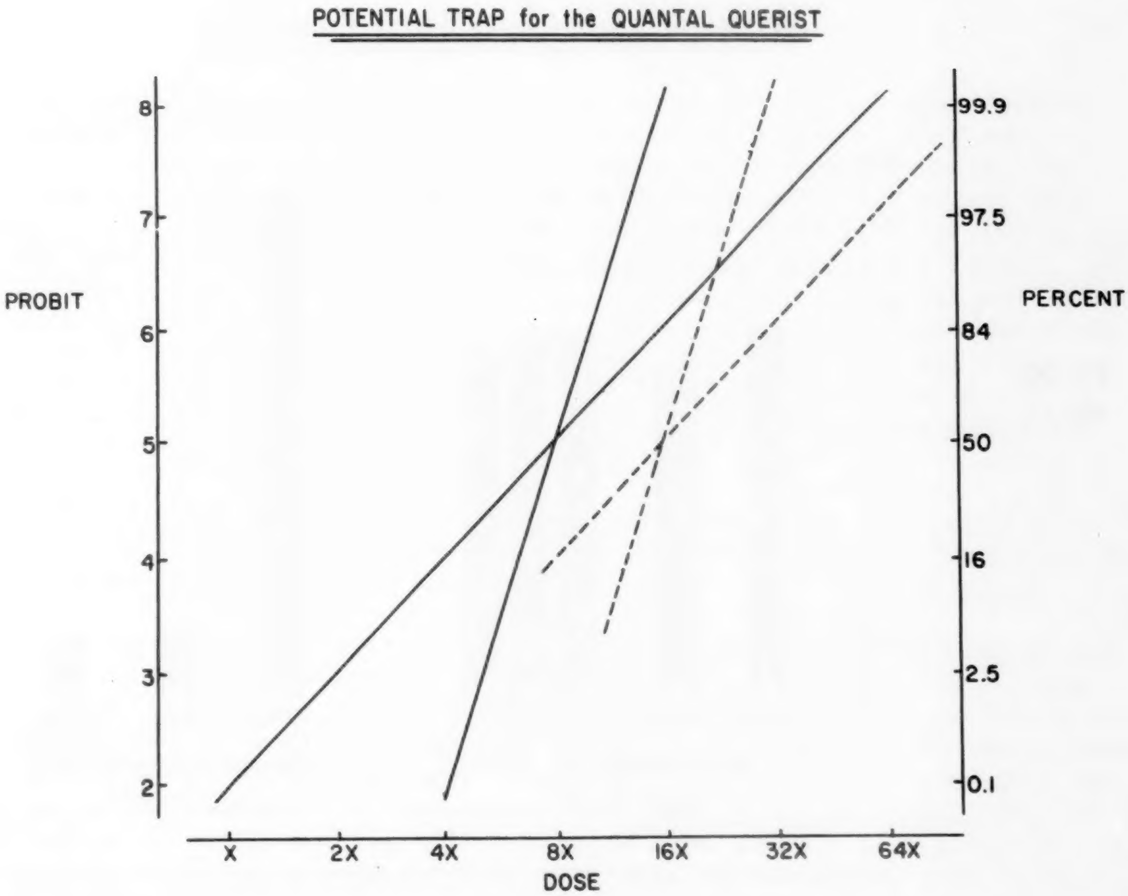

Figure 4. Comparison of the effects of nonselective inhibition of two quantal stimuli, to illustrate a potential trap for the Quantal Querist. See text for discussion.

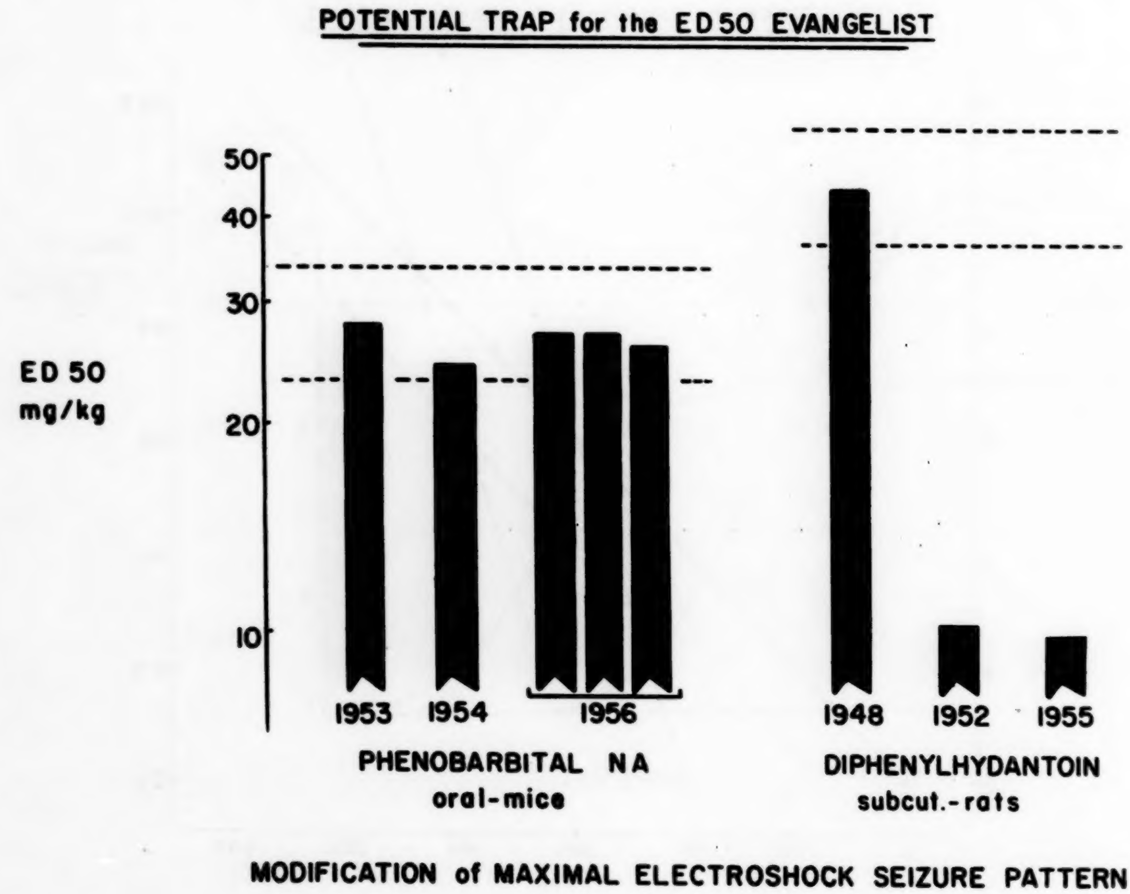

Figure 5. Tabulation of ED50's determined at intervals of several years in the same laboratory, to illustrate a potential trap for the ED50 Evangelist. See text for discussion.

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TUESDAY AFTERNOON DISCUSSION SESSION

T. C. Daniels, Chairman

As you recall, Dr. Holland placed a good deal of emphasis on energetics, metabolism, and the contributions of bio-chemistry to development of precise methods for determining mode of action of drugs. Dr. Swinyard, on the other hand, pointed to the limitations of the laboratory evaluation of drugs, made references to the fact that the definitive evaluation of drugs is a continuing process and that rarely do we have all the information that is available. Dr. Beecher brought out the problems concerning clinical evaluation, subjective changes that are difficult to evaluate, and discussed at some length standards to use for pain relief, etc. Finally, Dr. Fingl discussed the limitations of statistics and the hazards of statistical bias that may face those who would like to reduce their experimental findings, to, we will say, a mathematical basis.

Question: Dr. Fingl's presentation implied that statistical evaluation is a succession of pitfalls. He has appeared to emphasize the negative rather than the positive approach to statistical application.

Dr. Fingl: I hope I didn't create the impression that I am a statistical hayseed, a skeptic, and a disbeliever, because that is certainly not true. And certainly, should there be errors in statistical design which I criticized, I did so with the understanding, on my part at least, that with these old frames there is probably an adequate design. The error comes in not recognizing the limitations of that design. I hope that I have emphasized previously that a preappraisal of an experiment is well worth the time spent. Your profit usually comes in the fact that you can then redesign your experiment and make it more efficient or that you will redesign it so that you really get the answers you seek. How often has one of us done an experiment, bothered to calculate it, come up with some answers and then decided that back in the planning stage we made an assumption which we wished we'd not made, or wished we'd used three doses instead of two, or wished we'd used ten animals instead of eight, etc. I think my big plea for pre-evaluation is the thing.

Perhaps I sell statistics shorter than most people in that I always emphasize that statistics tell you nothing more than the probability of a certain set of results occurring by chance. You have to start from this point with your biological understanding and decide just what this probability means to you. At this point you leave statistics completely and go into biological common sense. As Dr. Beecher said, statistics is not a substitute for common sense and I heartily agree with him. At stages though, you have to use statistics to back yourself up, or to assure yourself that you haven't let your common sense lapse, but you have to rely on your judgment as biologists to interpret what you get from statistics.

Dr. Holland: I would like to make a comment. I think mathematics has made two contributions, evaluation and analysis with the use of the mathematical method. I can illustrate this and show you that mathematical analysis is much more intellectually satisfying. Take a typical dose-response curve. You can see the beauty of the Michaelis hypothesis when you've looked at his data. He said, "Now, can I have some idea and develop that mathematically which will predict the form of this curve?" He assumed that a drug reacted with something called a receptor to form a complex, and this produced a response. From this he derived a very simple mathematical relationship which then had a very profound influence on our thinking in pharmacology. This is what I call analysis, the real beauty of application of mathematics to pharmacology rather than trying to fit data from poorly designed experiments.

Question: Toxicity is a matter of overdosage or of immunulogical sensitization, or of idiosyncrasy. Biochemical defects are beginning to appear as bases for idiosyncratic reactions to drugs. Thus, therapy is going to be more and more based on an understanding of a biochemical deficiency situation.

Dr. Holland: In different individuals the absolute amount of an enzyme might vary. From the work of Brodie at the National Institute of Health a number of enzymatic reactions have been shown to detoxify various drugs. It is quite obvious that if there were a variation in the amounts of these enzymatic components we would certainly expect a variation in the sensitivity and maybe some people would be more sensitive. This may be interpreted on an enzymatic basis as a deficiency in the particular enzyme which destroys this particular drug.

It doesn't answer the problem merely to say that a certain enzyme is detoxifying or reacting with a drug to produce a change in structure so that a drug ceases to be inactive. The remaining problem is, how does the drug produce its effect in the first place? That's the basic problem, and I ask, is this enzymatic? Most biochemists today, the rigid followers of this particular concept, would indicate that every biological phenomenon is one of catalysis. So even though we could explain the biochemical observations that an idiosyncrasy is due to the deficiency of an enzyme, we still haven't answered how the drug itself really exerts its effect.

Dr. Fingl: While we are talking about the effects of drugs on specific enzymes I would like to get Dr. Holland to expand on something he touched on briefly earlier. He classified effects of drugs into two categories, selective and nonselective, and referred to the fact that nonselective would be drugs acting upon the main energy-yielding systems in a cell; that if we have selective drugs we must look elsewhere than in the main glycolytic monophosphate shunt, or Krebs cycle system. I would wish Dr. Holland would expand on just where or how he visualizes the specific effects of drugs.

Dr. Holland: I think the difficulty here is the fact that I attempted to classify this on a biological basis. In order to do this we have a limited number of functions and we know that certain drugs affect all functions. Dinitrophenol is a typical example. If you read the literature you see that it's an excellent growth inhibitor. It also depresses the heart beat. It also affects contraction, it also modifies bioluminiscence, so from the biological point of view I can call

this nonspecific drug action. Now, if we go to the chemical level this classification will not hold up. We have to redefine it in terms of specific and nonspecific inhibitors of enzymes, but the basic philosophy is the same because we find that when we speak of a specific enzyme inhibitor, it only inhibits a large number of enzymes in low concentration.

This brings up another important problem, the philosophy, or method of approach, the three P's of any endeavour: a philosophy, a purpose, and a policy. There are two ways to look at any phenomenon. One is what we call the phenomenological approach, the other the mechanistic approach. This is well illustrated in physics. Take a gas and put it in a bag. Now there are certain properties we can assign to this. We can assign a form, we can say it has a certain volume, a certain temperature, and a certain pressure. We can make no postulations about any hidden occurrences but we can predict the behavior of this bag of gas when we alter these variables, so the thermodynamist says that PV is equal to NRT, making no assumption about the structure of the gas. This is what we call the thermodynamic or phenomenological approach. Another is a mechanistic approach which says that this gas is composed of atoms in constant motion bombarding the sides of the container. If we use that we can derive the same equation. Now, we have the same problem in biology. We can look at a biological system in two ways--leave it undisturbed, use a thermodynamic approach which I prefer to call the physiological approach, or we can take the mechanistic approach, that of the biochemist--and from both of these we can get information. Now this morning I used primarily the physiological approach to classify the mechanism of drug action, but you can also do it equally well at the biochemical level.

Dr. Fingl: What I was trying to drive at is one example, the action of epinephrine. On some types of smooth muscle it causes an excitatory, a contractile effect. On others it causes an inhibitory relaxation. Can you foresee tentatively, or speculate on how this would be explained in terms of one common enzymatic mechanism for epinephrine?

Dr. Holland: Let me give the audience another example of Dr. Fingl's question. We know that acetylcholine, another mediator, depolarizes the motor end plate. But it also hyperpolarizes the myocardial nerve muscle junction. How are we going to explain this? If we take the biological approach again, there is one more point to remember. In general the myoneural junction, that is striated muscle, has a single innervation, whereas the myoneural junction in the heart is doubly innervated. We are failing to appreciate the influence of one mediator, that is norepinephrine, on the effects of acetylcholine, and vice versa. I think this is the reason that epinephrine excites, in some tissues, and in others it inhibits. This may well depend upon the presence of the other mediator, acetylcholine. This is just a hypothesis that may answer you.

Dr. Leake: There is another mechanism entirely involving energy exchange that may not be mediated by enzymes at all. There is the possibility that a quantum of energy may jump from one compound, a drug, to a molecule of the cell. For example, to explain the carcinogenic action of some steroids, one would assume such a quantum jump. That, as I see it, involves no enzymatic action.

Dr. Holland: I think that's quite right, but that's the problem with any new concept or idea that becomes overworked. After a period of years people have to sit back and distill from it what's the truth. Now the question is, is every biochemical or physical reaction that occurs in the living system enzymatic? I certainly think it's not because molecular forces other than a breaking of chemical bonds exist. We have electrostatic, Van der Waals forces, etc., which themselves may actually produce these effects. Don't get confused if enzymatic reactions are much faster than these. The fastest of all reactions are those of simple diffusion. They have the lowest activation energy. One thing I would like to add. What I've introduced here is the energy concept which is rather old and really started with Himholtz. He was of the opinion that this concept was not violated by a living system so we can have any energy yielding reaction. Those are the only three types we can have, yielding, transfer and storage, and utilization. If someone in the future finds still another system more important in glycolysis, these principles will still hold, because they're based on thermodynamics. It used to be argued that the transfer of mass and energy violated this principle but when Einstein showed that $E=mc^2$ that solved the problem.

Dr. Leake: You mentioned depolarization. Is there any evidence at all on the relative depolarizing capacity of molecules of drugs on the standardized preparation?

Dr. Holland: Not to my recollection. It is the only thing on which I can speak with authority--the fact that acetylcholine is a cation and it exhibits many properties that you would expect of a cation when you put it on a catimic exchange resin. It is interesting to note that acetylcholine is a mediator at the adrenal medulla. In addition, at the pH of the adrenal medulla cells, epinephrine exists as a cation, so this may well be a cation exchange process which is certainly not enzymatic but extremely rapid, because coulombic forces and forces of diffusion are involved which have very low activation energies and therefore are extremely fast.

Chairman: Dr. Holland, are you suggesting that epinephrine attaches by virtue of being a cation to the enzyme system, or what is your inference here?

Dr. Holland: I'm trying to emphasize that I believe that a number of receptors, or what we call receptors, may well be enzymes. I think I can illustrate what I am talking about if you take into consideration that there are two processes involved in what we call an enzymatic reaction. There are two important things involved, the enzyme and the substrate. A reversible reaction forms the enzyme-substrate complex from which we have products. There are two reactions involved here. One a physical process, and the other is a chemical process. Now the interaction of drugs with receptor is the physical process. This produces a change in the structure of the enzyme. Then we have a much slower chemical reaction compared to this reaction. The products have to diffuse away from the surface before you can measure them. There is good evidence in the case of actomyosin, in the presence of ATP, that a change in structure occurs upon immediate combination of actomyosin and ATP, followed later by conversion of ADP plus phosphate. Now this is what the pharmacologists, I believe, would call receptor reaction.

Chairman: Are you suggesting that the mode of action of actomyosin is a removal of ATP?

Dr. Holland: No, I think the basic reaction is the combination of ATP with the protein in a sudden energy exchange like Professor Leake speaks of. The energy is transferred before we see any products.

Question: Is it possible that the combination of acetylcholine and cholinesterase is similar to the combination between actomyosin and ATP, producing depolarization at the motor end plate, with the chemical process that follows being the hydrolysis of the acetylcholine?

Dr. Holland: The only thing we know about acetylcholine is it changes cell permeability. That's the only thing we can say on a molecular basis; on a biochemical level. We don't know of any other thing that it does. But this may well be like the tick of a clock. When we hear a clock tick we know something is going on, but we don't know exactly what it is. Now the question arises, is the permeability change a primary or secondary effect? We all believe that we can convert the energy of glucose into osmotic energy to maintain concentration gradients. But the question has never been raised, can we reverse the process and convert osmotic energy into chemical energy? If ACh does increase cell permeability then the free energy of the concentration gradient becomes effective. Could this be used to release another substance which produces the effects that we observe?

Chairman: Now we have spent a fair amount of time on Dr. Holland's paper dealing with the biochemical approach to pharmacology. We want to allow time for a discussion of the laboratory and clinical evaluation, the experimental design.

Dr. Leake: What are the criteria of what we call "normal"?

Dr. Beecher: Well, I think one can set up an operational definition of the normal. I suppose the simplest thing would be that the individual functions in his environment in such a way as to be a productive citizen.

Dr. Leake: I don't believe your answer is scientific.

Dr. Beecher: Well, I don't think your question is scientific.

Dr. Leake: What I want to know is, what does one mean by normal? Are we talking about an "average" measurable physiological function, or an "average," a concept or abstraction that we call "average" measurable physiological function? I think we have to define more closely what we mean when we say "normal."

Dr. Beecher: I think you have answered your own question and very soundly, too, as long as one will indicate what the environment was and what the situation was. That certainly has to come into this. I have not the slightest doubt that personality, type, and conditioning have a tremendous amount to do with the type of reaction which one gets. I illustrated that with morphine when I showed that the majority of people were made dysphoric by the drug whereas the drug addicts in the majority were made euphoric by this drug.

Dr. Leake: But can you measure physiological functions in such a way as to show deviation from the "normal"?

Dr. Beecher: If we can't, we are certainly spending a lot of money for nothing. We have a project going and have had for about three years now, and we are trying to correlate personality type with drug action and we are having some success. It's a long hard road to hoe, but I think this is an indispensable job that must be done if we are to progress soundly in this field.

Dr. Leake: I have in mind something else. An average individual person responding in an average way to the environment has an average blood pressure for his age, or his circumstances, or an average respiratory rate, an average pulse rate, an average muscle tone. You can't measure that very well but that may be very important in this whole business. What about average speed of response to a given stimulus? Now that together comprises in one way an average person with measurable physiological activity. Now my point is, how does his personality shift, as it were, or his mood shift in correlation with any one of the combinations of these measurable physiological functions?

Dr. Beecher: Well, of course, unless you are willing to work with tremendous quantities of data, which would be prohibitive from my point of view, one would have to use correlated data, crossover data, and having done that, a great many of these idiosyncrasies of a given individual cancel out. You're using the same individual as his own control; you're pitting two drugs against the same individual, and that gives you a comparison of two drugs. When you do that with a reasonable group which varies according to experiments you are working with, whether there are 25 or 50 people, one can cancel out a great many of these improbabilities, and I think one must do it. I somehow fail to understand what he is talking about because to me it's so obvious that one must cancel out all this conditioning, what one might call Pavlovian aspects.

Chairman: In the case of analgetic drugs and perhaps hypnotic drugs, speaking of the normal, you would be somewhat concerned with the tonicity of the individual. I am speaking here of nerve tonicity which is a very vague expression but perhaps conveys the meaning.

Dr. Leake: You see we have no satisfactory physiological way of measuring muscle tone. In general we say that an individual who is under tension, or anxiety or excited may be under real increased muscle tension. On the other hand, a person who is quiet and relaxed and calm has less muscle tension, but we have to work out a way of measuring that.

Dr. Beecher: I suspect that we can, but don't you suppose, Professor Leake, that in the background, personality type has a lot to do with why one man has more muscle tension than another. That's only one item, of course; surely there are a great many factors that we have never got hold of but we must grope toward them.

Dr. Leake: Perhaps we should consider activity of the thyroid in influencing the response to the drug. That also has an effect on some of these measurable physiological functions. The effect of activity of the thyroid can be measured pretty well in terms of metabolism, etc. It seems to me that we could more satisfactorily take into account a lot of these measurable affairs. I am reminded of the administration of general anesthetics where we do take the blood

pressure, pulse and respiration and with these observations can judge pretty well where the patient is in anesthesia.

Dr. Beecher: Well, we like to think we can, but I am reminded of an English surgeon who had a rather sharp tongue and a bright wit. His anesthesiologist was having some trouble with a patient on the table. The patient was moving around a good deal and Sir Wilfred looked over and said, "Sir, if the patient can stay awake, I should think you could."

Dr. Kirby: Who prepares the scoring of subject response in your experiments? Do the research men themselves handle this?

Dr. Beecher: We don't do it in quite that way. We have technicians who have no interest in or knowledge of what we are looking for; technicians who are allowed to ask only very stylized questions. It would be very bad to have those of us with vested interests doing this.

Question: Do your patients realize that they are subjects of experimentation?

Dr. Beecher: No, they don't and that makes a great philosophical problem because, if you read the Nuremberg trials, you know that of the points set up about human experimentation, one of the most important was the very first one--that all subjects must be informed of what's being done to them. Now, every doctor knows that he violates that number one thing in the Nuremberg trials, and how to get around this or how to rationalize it makes a philosophical problem, perhaps not pertinent to this data.

Dr. Swinyard: I would like to direct this question to Dr. Beecher. I think there are many of us that have followed his work more or less closely and time to time may gain the impression that he feels that the only and best way to evaluate analgesic drugs is in the human. Certainly I indicated in my presentation this morning some of the limitations of laboratory procedures for evaluating analgesics. You heard him just mention the fact that there are real pitfalls in the testing of these agents in human patients. I would like to hear him discuss this topic and get his views on some of the pitfalls that may occur in the evaluation of these agents in humans and perhaps point out some of the high points in the application of the laboratory testing of analgesic agents.

Dr. Beecher: Almost sixty years ago a working hypothesis was laid down. I wish I could take credit for it, but I can't. This hypothesis grew out of a book by Marshall on Pain, Pleasure and Aesthetics. In 1895 Strong read Marshall's book and made the crucial assumption which Marshall had failed to do. He presented this hypothesis without any data to support it, but we have been ardently working throughout some years and gathering data to support this and it does seem like a very tenable point of view which is this--that all suffering consists of two main components. The first of these is the original sensation, and secondly, the psychic processing or reactions to the original sensation.

Now one very basic concept and assumption made by almost all experimentalists in this field of appraisal of analgesic agents is that there is a pain threshold which is constant from man to man, constant within a given man from time to time,

and secondly, that this pain threshold will rise in response to the administration of analgesic agents. Now that goes back to Hardy, Wolfe and Goodell's work with radiant heat techniques. It also is an assumption made by those who use electric shock to the teeth, pin pricks to the skin, etc. I am not wishing to pick on one method, but all human experimental pain methods have that assumption in them.

The difficulty with that is that some very careful observers, even with carefully designed experiments, were not able to distinguish between 15 mg. of morphine and the placebo. That seems rather shocking. But at the present time I can tell you that 15 groups around the world, mostly from this country, have utterly failed to confirm this hypothesis that the pain threshold is demonstrably sensitive to the action of analgesic agents. So at the present time I think we can make one conclusion. While I don't say that they have not been shown to act on the original sensation I would like to say there ought to be a demonstrable relationship between the action of analgesic agents and the pain threshold. But there just isn't in the hands of 15 careful groups. Tom Butler is one of the most careful workers in this field I know of. He utterly failed with the most careful work to demonstrate any relationship, and that's true of 14 other groups.

For the moment, at least, we have no right to say where an ending is stimulated and the nerve impulse starts out and ascends to the central nervous system, that this is directly modified by morphine. But what we do know is that a great many things can alter this psychic process in the reaction phase. Now, I'd like to be very careful in defining that. If you burn your finger in a flame, you withdraw it. Now that's one kind of a reaction to pain, that is a skeletal motor reaction. I'm not talking about that. For that matter the building of a hospital is in response to the need for the treatment of pain and a kind of reaction to pain. I'm not talking about the autonomic effect, the change in heart rate because your heart rate increases when you smash your finger, etc. These are all consequences of pain. I'm talking about an intimate part of the pain experience that can entirely block perception of pain. This is not all in the same category as the skeletal motor reaction or the autonomic reaction. This is an inseparable part of the pain process.

We have a pain, we have an injury and then we have psychic processing of the meaning of pain to us, as a significant thing. I want to give you some evidence of how important this is. First, I want to show how very important the action of the placebo is.

A placebo, I think, can only work through its effect on psychic processing. We observed in some seven of our own studies that placebos effectively relieved pain or did various other things in about 30 per cent. I looked among eight studies of other people and found that this was also true in the wonderful paper by Evanson and Hoyle, published 24 years ago on severe carcinoma, and in this they found the placebo relief in 38 per cent of the cases. That was confirmed by Gold's group. Then Jellinek found that headache was relieved in 52 per cent of the patients by placebos; Gay and Carlisle found that seasickness was completely relieved in 30 minutes by placebo. And so it goes. In the end we found that in more than a thousand subjects, in some 15 studies, placebos have an average effectiveness of 35 per cent. Recall that I had said earlier that the maximum effect I could get with a very large dose of morphine was 75 per cent.

In other words, on the average the placebo takes care of half of the pain relief, even with a wonderful agent like morphine. If we were to go on and study this thing further, we'd find that when stress is very severe, placebos are much more effective than this. I won't take time to give you the details now, but a placebo would relieve 77 per cent of the pain of a group who are having very severe pain, whereas when that pain had been diminished a great deal, a placebo would relieve only 29 per cent. So we have some evidence at least that the effectiveness of a placebo would be directly related to the degree of stress. One can only understand these things in terms of the psychic processing component. As small boys we probably all had fist fights, we got hurt, we got bloody noses and scratches and cuts, and we felt no pain until it was all over, until our mothers began to sympathize with us, perhaps. We know that emotion can block pain; that's common experience.

Here is another type of data which indicates that this psychic reaction of processing things is terribly important. During the war I had an extraordinary opportunity to study freshly and badly wounded men on the Anzio beachhead. Anzio, as some of you may know, was a pretty bad place and there were shell crashes to be heard or shell flashes to be seen at least every 60 seconds day and night for many, many weeks. It was a place of constant bombardment. Anybody who was there had an idea that he might die. Soldiers who were wounded were brought in; soldiers who had penetrated chests or penetrated bellies, compound fractures of the long bones, who were clear mentally, who had no morphine at all in many cases and in no case within four hours; men who were not in shock, who were cooperative. Only one quarter of these men had enough pain, in answer to a direct question, to say they wanted anything done about it. Three-quarters didn't have pain of any degree, enough to require treatment.

I repeated that study with civilians who had had surgery (if there are many surgeons in the group I hope they will forgive me when I say that I think the average citizen considers the necessity for surgery disastrous, a calamity). These civilians who had much smaller wounds, much less tissue trauma, with a smaller number of disturbed pain endings, quite obviously had enough pain to want to be relieved in more than 80 per cent of the cases. The civilian hated his wound, he hated everything concerned with it, he had a lot of pain. The soldier considered his wound a ticket to the safety of the hospital; he was going home, the war was over for him, the wound was a good thing. I can't escape the conviction that the significance of the wound is the thing that determines the suffering. I wasn't the first to observe things like that. A man named Dr. Guthrie, running about the peninsula wars in Europe in the 1820's, said that of two men suffering the same detriment from a wound, one man would "writhe with pain whilst the other smiled with content."

Taking all these things and keeping them in mind, then we must say that this thing I'm calling the psychic processing of sensation must be important. One may be able to break it down into a lot of things.

So much for man! How is man different from animals? I said I didn't believe that experimental pain in man was useful, as usually applied, for the appraisal of analgesic agents. Why? Because this is a very different situation. There isn't enough of a psychic reaction compounded in here to show any change perhaps, but animals are another thing. I don't mean to decry Hardy, Wolfe and

Goodell, the work of Dr. Gross and various others, but I think with animals there's no question. Animals do respond, at least as far as one can judge by their reactions. That's all we can judge by--the tail flick of the rat, the skin twitch of the dog, etc. There is a direct relationship between their thresholds and the actions of analgesic agents. To an animal all pain is serious and significant. The animal, we presume, cannot distinguish between experimental pain and pathological pain, so for our purposes I think we are on safer ground when we use what one might call "real pain" as opposed to contrived pain because this psychic factor here is of such overwhelming importance, we're surely going to be led astray if we depend on it in man. We can get useful information out of animals. I don't think we can from man the way we usually apply these techniques. If we put a great anxiety component in here, one can begin then to get a labile or a demonstrable sensitiveness of the pain thresholds to these agents, but we have to bear in mind that we're dealing with a very complex situation.

Chairman: Dr. Beecher, where does hypnotism fit into this general picture?

Dr. Beecher: There's no question in my mind that hypnotism is very effective and I think that has been demonstrated beyond any possible doubt. I assume that's a modification of this reaction. One's reaction is influenced in a way that pain is prevented. There have been numerous cases where individuals have had surgical operations carried out. I can understand how a stoic might be able to restrain a cry, but I'm sure that a stoic could not control his heart rate, and the heart rate goes along without any rise whatsoever in this case. I'm sure that hypnotism is a fact.

This psychic reaction begins probably even before the central nervous system is reached. It certainly begins the minute these agents hit the cord. Wikler has shown us very nicely in the crossed-extensor reflex where several neurons were involved, where there is a lot of after discharge, that these reflexes are sensitive to the action of morphine. They are depressed by morphine, but if there's not much after discharge, these actions are not depressed by morphine; they actually are heightened. We know from evidence of this kind that processing does begin early. Central control of peripheral reception is just coming into prominence. Certainly the central activity, the downward activity can influence these pain receptors. There's a good deal of evidence of that kind which is surely pertinent to this and in that case we must allow that the processing begins at a very low level.

Dr. Keasling: The use of analgesics is accompanied by various objectively measurable side effects, for example, the depression of respiration. Is it not possible to use these side effects--perhaps I should term them secondary effects, as an objective index of relative activity between drugs?

Dr. Beecher: I agree with you that perhaps a better term would be primary effects and secondary effects. Sometimes when we use morphine we use it for the primary effect of respiratory depression. For example, before we had other ways of paralyzing the respiration during certain thoracic operations, we used to inject morphine intravenously in those persons during anaesthesia. Respiratory depression was the primary thing we were seeking in that case. You're quite right in that what you're seeking may differ from one time to another. To call nausea

and vomiting a side effect I think is all right. I proposed to the committee on drug addiction several years ago that we set up an animal screening method which would depend on the power of analgesics to depress the respiration. It gave me a certain amount of malicious glee to find that someone blundered into that very thing and was quite successful in screening in that way. But that falls down as all screening methods do. It would fall down with dihydrocodeine because in the 30 mg. dose without exception, there is no depression of respiration in man.

Chairman: Dr. Swinyard, would you like to suggest or comment on this?

Dr. Swinyard: Perhaps what Dr. Keasling is thinking about is the fact that we do see in certain groups of agents certain of these effects, in many groups of compounds. I'm thinking, for example, that tridione was originally introduced as an analgesic and tested as such. I'm thinking of the well-demonstrated effect that phenurone, although it was introduced as an anticonvulsive, has been shown to induce analgesia and loss of pain sensation in certain individuals. We got interested in this problem and found that there was a certain analgesic effect in all of the anticonvulsant compounds. I wouldn't say that one could screen for anticonvulsive activity by searching for an analgesic, but I do think that there may be run in series some of these secondary effects. Let us say they are present in many of these compounds.

Question: In regard to the direct relationship between these analgesic responses of man and animals, is this not a fortuitous phenomenon?

Dr. Beecher: Well, there are many places where it breaks down very badly. It has been very useful though, and I think Dr. Keasling will bear me out on that. The only place that it's broken down with powerful analgesics that I know of is with N-allylnormorphine which has by common agreement no analgesic power in animals. There was one early study. Ross Hart, I think, thought it did have, but no one was able to confirm that. Most people have failed to show any analgesic action of N-allylnormorphine in animals, so if it exists it would easily have been missed by the majority.

Chairman: Dr. Holland, would you care to comment on the biochemical aspects of the analgesics.

Dr. Holland: We cannot reduce the psyche to something we can measure accurately. This still remains to be done.

Dr. Beecher: I don't know what you mean by the "psyche" or what you mean by "measure accurately," but I showed this morning we can deal with pain problems with an accuracy of about 10 per cent, which is about as accurate as one can deal with gross objective things. It seems to me that this whole business is so awfully important because the welfare of the human race depends on turning these things into science.

Dr. Holland: We accept that the philosopher's concept of the scientific method is observation, experimentation and hypothesis. My point of view is that we have no way to control the psyche.

Dr. Beecher: But I think one can cancel out these differences between men by proper design of experiment.

Dr. Holland: I would like to ask about this type of experiment. If we took a group of people, gave them barbiturates and then tested a second drug, would a placebo have any effect? Could we control our patients by the use of drugs, establish a background, then test other drugs with meaningful results from the placebo?

Dr. Beecher: I think we have to deal with groups here. As Professor Leake points out, we're dealing with averages, not only in terms of the type of people, but in terms of responses. But that doesn't lessen, I think, the importance of getting at these things through these lines. I think that it's very wrong to think that the basic science quadrangle is the only place where basic science is carried out. I have just been getting together a series of lectures to demonstrate that sometimes basic science can be advanced only in the presence of disease. I think that the physiology of the endocrines could not possibly have been advanced without disease, nor could we have learned about the neuroanatomy of the central nervous system without having a lot of data from cerebral vascular accidents. The clinic has been a rich place in furthering basic science in the classical sense. Now just because when you begin to deal with what you call the psyche you begin to run into heavy weather doesn't mean that we shouldn't keep on looking, seeking, in this area, and I think we can work with precision.

Dr. Swinyard: I think, Dr. Holland, that one might have to choose between the possibility of reducing the psyche to the point you have indicated and the complexity that would be produced by introducing drug combinations. Personally, I believe I would elect to deal with suitable controls to nullify the effects of the psyche, rather than introducing drug combinations.

Dr. Beecher: There's one thing that I should have added. We made quite a study of placebo reactors. They are very interesting customers. This doesn't mean that once a placebo reactor always one, but there's a tendency in that direction that is very significant. We got to know about the characteristics of these people: they are 100 per cent churchgoers, they are the good citizens, their intelligence level is at least that of other people in the community, they are cooperative and helpful individuals. Well, that's only one little splinter in trying to break this thing down. Sometimes we can't show significant effects of drugs until we have screened out the placebo reactors. That is, one can heighten the degree of significance of difference greatly by screening out the placebo reactors. After all, you're not interested in the capsule, but the contents of the capsule. You're always deviled by what Colin White, the English statistician, said--that some samples are representatives of nothing but themselves.

Question: First, I would like to ask Dr. Fingl what constitutes potentiation and how does one measure potentiation? Secondly, how can we teach biostatistics to graduate students?

Dr. Fingl: I knew I would live to regret using an example in which I used the word "potentiation." I should start out by saying that I don't know the answer to either of your questions. I have pondered this problem of potentiation and

my first decision was one that was cowardly. That is, I would never try to define potentiation because it was just a hopeless problem. There are two reasons why I took this defeatist attitude initially.

The first has to do with the distinction between two words in the English language which we should be happy that we have and which we probably misuse occasionally. These two words are "action" and "effect." Dr. Walter Loewe, emeritus professor in our department, would be very happy to hear me repeating this age-old argument. We have to remember that we talk about the mechanism of drug action and here we use "action," thinking about something happening at the enzymatic level, or at the subcellular level. But we're stuck out in the periphery in measuring an "effect," which tends to muddle and confuse the issue, because we're not at the precise point we think we are. Very frequently this problem of potentiation boils down to a definition of the action level, and we're interpreting it at the effect level.

The second reason for avoiding the definition of potentiation is that having decided that I'm going to make a definition of it at one level or another I can define potentiation only in terms of being supra or infra-additive. Now I'm down to the problem where I have to define additivity at either the action or the effect level, and here I have to make some assumption about mechanisms of action in order to define additivity. If I get more than what I assign as being additivity, I will call it potentiation and if I get less I will call it antagonism. So the problem centers on two things; making a definition as to what is additivity, and secondly, making a choice between whether I make that definition at the level of effect and remembering what assumptions go into making these two definitions.

You can avoid calling it what you will or sticking your neck out in your definition by deciding whether you want to find simply a combination of drugs which is better than any single drug. You can simply look for a combination of drugs which produces a more effective therapeutic ratio. You can find something which is better because it has a more satisfactory therapeutic ratio without committing yourself to whether this is due to potentiation or a certain type of additivity. If I can get a certain intensity of analgesic action with less incidence or less intensity of side effects, and if I can get more favorable reaction with a combination or a more favorable ratio with a combination I'll consider it satisfactory and I won't question whether it's potentiation or not.

The second question I can supply equally unsatisfactory answers to in saying I don't know how to teach graduate students statistics or experimental design. I can tell you the things that do not work out. Telling them to go read a book which I found satisfactory isn't good. Having them come to me with some data and going over it and criticizing it doesn't seem satisfactory. About the only thing that seems to be good is continuous use, constant criticism and constant exchange of ideas. In other words, if you can force the newcomer to think of his own data, data that he has spent his own blood, sweat, and tears collecting and subjecting to analysis so he can see what's happening to it, perhaps this makes more sense than selecting one of your pet problems and saying, "Now I was confronted with this question; I designed my experiment in such a way and these are the conclusions I reached." Rather you should take the

individual's own data and rely on time and experience and lots of counseling to get across the ideas that you think are important. I have found no really satisfactory way to convince others except by the slow process of discussion.

Dr. Holland: There's an old story that goes around in Alabama that a fellow had a little restaurant and thought he'd serve some rabbitburgers. A gentleman walked in and had one. After he'd tasted it, he called the man over and said, "Say, mister, this is not rabbit meat; this is horse meat." He insisted, so the proprietor said, "Yes, you're right, there's some horse meat in there, but it's all right, it's still half and half--half rabbit and half horse." The customer said, "Will you tell me how you made it?" The owner replied, "Well, I cooked one horse and one rabbit." Perhaps this is what we call additive effects.

Chairman: The time for adjournment is approaching. We have been discussing this afternoon the laboratory and clinical evaluation of drugs and no reference has been made by the panel or anyone else as to the evaluation of addiction properties of drugs. I'd like Dr. Swinyard to lead off for just a short time and perhaps Dr. Beecher from the clinical side would have some remarks he'd like to make.

Dr. Swinyard: When you stop to think that we have great numbers of new agents introduced into therapy now that have subtle effects on the central nervous system and are taken in untold quantities routinely by untold numbers of people, then addiction is in reality a very important problem. Furthermore, I think that again I would be reasonably safe in saying that drugs which induce withdrawal symptoms have been detected for the most part in the clinic rather than in the laboratory prior to clinical application.

I think there is an approach to this problem that offers some degree of promise. A few years ago my colleague on my left, Dr. Fingl, in association with Dr. McQuaid, devised a technique whereby one could detect the withdrawal hyperexcitability in laboratory animals (mice) and show the effects of chronic administration of the barbiturates, alcohol, and other agents. More recently Doctors Fingl, Chinn, and myself have applied this to meprobamate and demonstrated withdrawal hyperexcitability following administration of this agent. With more experience with a greater variety of agents it's entirely possible that this may offer presumptive tests for drugs which hold potential addictive properties, or may induce withdrawal symptoms after prolonged administration of elevated dosage. Now this is going to mean that you've got to consider not only duration of treatment, but you've got to consider intensity of treatment. Dr. Beecher, do you want to comment on that?

Dr. Beecher: It's out of my field of competence, I'm afraid.

Dr. Way: What is your definition of addiction, Dr. Swinyard?

Dr. Swinyard: I was not defining it, Dr. Way. I was trying to stay away from that. I was defining withdrawal hyperexcitability.

Chairman: Now these withdrawal symptoms that you speak of, Dr. Swinyard; is this merely hyperexcitability on the part of the animals upon the withdrawal of the drug or what symptoms are you referring to?

Dr. Swinyard: The technique that Dr. Fingl introduced and which I think is very real, is to determine the threshold for "psychomotor seizures" (low-frequency electric shock seizures) then treat the animals with the drug for a period of two weeks at appropriate intervals, at the appropriate dose level, carrying along at the same time a control, then suddenly terminating therapy and measuring over a period of the next four or five days the low frequency electric shock threshold of those animals. This will show increased excitability.

Dr. Fingl: I don't know that you can really avoid breaking addiction down into the various components that have been tried. For example, I think it's one thing to talk about the tendency of the drug to produce euphoria or other sensations which make a person desire to have the drug repeated. I think it's another thing to talk about capacity or potentialities of the drug to produce withdrawal symptoms after chronic administration when the administration is stopped. I think it's something else to talk about these habit-forming potentialities of the drug, etc. In addition, hasn't the methadone field shown us two other variables which tend to make one cautious in this field? If I remember correctly, Dr. Brody, very early in the methadone era, the Michigan group reported that methadone was not addicting in monkeys. This created some stir until it was shown that in those early days the people of Michigan were subject to taking week-ends off. The moral to be gained was that whenever you're working in this area, you don't want to rely on once a day administration five days a week or six days, but rather when you're talking about chronic administration you really mean chronic and don't let them up at any time. So here we come to one variable which just means that when you're looking for addiction liability or more specifically, let us say physical dependence, this is one trap. Another trap has been demonstrated by the Lexington group in that other characteristics of drug action, its duration of action, etc., have to be taken into consideration. For example, the withdrawal syndrome upon withdrawal of methadone is much less severe than the withdrawal you see when you administer nalorphine. The explanation put forward by Wikler is that the effect of methadone wears off slowly in the one case so that the withdrawal syndrome is never as intense as it is when you stop it cold with nalorphine.

Question: Are you suggesting that addiction liability and physical dependence are separable terms?

Dr. Fingl: You have to make a decision as to what you define as addiction liability. Is it the intensity of the withdrawal syndrome per se after you withdraw a certain dose? Is it the likelihood that the patient will want to repeat the medication so that he will develop some degree of addiction, or is it the severity of the withdrawal syndrome in proportion to the amount of analgesia that he would have had to produce that degree of withdrawal? It backs down to defining what you mean by addiction liability. There must be a relation back to something else. The severity of the withdrawal is just one variable and has to be related to another to be meaningful, either dose or dose required for analgesia, or something else--at least in my opinion.

Chairman: I want to express thanks to the members of the panel, Dr. Swinyard, Dr. Beecher, Dr. Fingl and Dr. Holland for having presented a very stimulating program during the day. I want to thank each of you for your attention.

Wednesday Session

INTERPRETATION OF DRUG EFFECTS ON THE HEART

T. C. West

Chairman

BASIC CONCEPTS OF CARDIAC PHARMACOLOGY

W. C. Holland

Vanderbilt University

Biochemical Considerations

Mention has already been made of the processes within the cell which are responsible for the availability, transfer and utilization of energy. With respect to the heart, a number of questions have to be answered. What foodstuffs feed the energy dynamo of the heart? In what proportion does the heart use them? What general conclusions on the mechanism of disturbed cardiac action can be drawn from changes in the utilization of foodstuffs by the heart?

Metabolism of heart muscle has been studied in tissue slices, on the heart *in vitro*, and finally in the intact hearts of humans. Each of these methods has certain advantages and disadvantages. Using tissue slices, the stepwise fate of foodstuffs through metabolic pathways can be followed; but there never is any real proof that processes observed in these unnatural conditions actually take place in the intact organism. For studies on the whole heart kept alive outside the body with artificical systems, only acute changes can be followed. Metabolic studies carried out on the intact human or animal heart *in situ* have the disadvantage that individual enzyme sustems cannot be individually explored. But *in vivo* studies have the advantage that they are carried out in whole organisms and under physiological conditions.

The technique employed in the study of cardiac metabolism with intact human and animal hearts is based on cardiac catheterization of the coronary sinus.

Using catheterization of the coronary sinus, it can be shown that the blood flow through the heart muscle is only a relatively small percentage of the total output (8 - 10 per cent). In contrast, the kidney receives about 25 per cent of the total cardiac output.

The heart is a working muscle, constantly demanding oxygen. The demand for oxygen is expressed in the large amount of O_2 which the heart muscle extracts from arterial blood. The oxygen extraction is almost maximal even in the normal working heart muscle. Since the extraction of oxygen is almost maximal at "rest," the only means on which the heart can rely to increase its oxygen uptake is through an increase in coronary flow. When for some reason, such as narrowing or obstruction of one or more coronary arteries, the flow of blood to the heart muscle cannot increase, the resulting O_2 lack in heart muscle produces the symptoms of coronary insufficiency with pain on exertion being the predominant complaint.

Using catheterization of the coronary sinus, it has been shown that the heart can utilize considerable quantities of carbohydrates, fats, ketone bodies,

and amino acids. Assuming complete oxidation of carbohydrates the aerobic metabolism of foodstuff in man could account for approximately 35 per cent of the total myocardial consumption. The main contribution to oxidative metabolism of the heart therefore comes from noncarbohydrate material. Myocardial uptake of fatty acids is particularly great after a high fat intake, suggesting the possibility of storage within the heart muscle.

It is likely that the relationship between utilization of carbohydrates and noncarbohydrate material is influenced by their relative availability and by the ability of the enzyme systems of the heart to catalyze carbohydrates.

In recent years, considerable information has accumulated regarding the alteration of metabolism of the heart in failure. For the purpose of our discussion we shall attempt a classification of heart failure based on the energy concept and information presented in Figure 1 (See Table 1).

The most interesting type of failure from an academic and clinical point of view is congestive failure. This clinical condition can be effectively treated with the cardiac glycosides while the other types are not affected by these drugs. They are best treated by removing the underlying causes, if possible, of the disturbance.

In recent years, considerable information has accumulated regarding the alteration of metabolism of the heart in congestive failure. The results of studies indicate that in congestive failure, the myocardial O_2 consumption does not differ from that obtained in normal individuals. Calculations of the myocardial or consumption gives values of 9.1 cc/100 gram/minute in the normals and 9.2 cc/100 gram/minute in patients with left ventricular failure.

Substrate utilization appears to be quite normal. No significant differences in myocardial usage of any of the base foodstuffs can be demonstrated in patients with congestive failure.

Further studies have revealed that there are no significant differences between the content of "energy rich" phosphate compounds in hearts of patients with congestive failure and normals. The best evidence available points to a defect in energy utilization.

The findings obtained on the effects of digitalis on the metabolism of the human heart are in agreement with this interpretation. The glycosides appear to produce no significant changes in myocardial O_2 consumption or in total foodstuff utilization. Furthermore, they have no effect on oxidative phosphorylation and the quantity of energy phosphate compounds in the normal and failing heart. These findings suggest that the improvement in work capacity of the failing heart, resulting from the use of cardiac glycosides, must be the result of their action on energy liberation or more specifically it must result from their effect on the contractile proteins of the failing heart muscle.

The nature of the basic reaction between the cardiac glycosides and heart muscle is not known, although actomyosin and K ions appear to be involved. Mallov and Robb found that actomyosin solutions exposed to cardiac glycosides

Table 1. Myocardial Failure

I. Disturbances in energy yielding reactions

A. Beri-beri heart disease

B. Myocardial O_2 lack and anoxia and anoxin

1. Shock

2. Anemia

3. Coronary occulsion

4. Hypothermia

C. Thyrotoxicosis

II. Disturbances in energy utilizing

A. Congestive failure

before testing showed better spreading on surfaces and a greater rate of shortening than standard untreated preparations. Horvath has shown a direct action of cardiac glycosides on the polymerization of actin, the step in the sequence of reactions leading to actomyosin formation in which the energy of ATP is assimilated. However, there is evidence that this is a nonspecific steroid effect. On the other hand, Szent Gyorgyi believes that the glycosides effect a more efficient utilization of energy by providing a favorable internal ionic environment for the formation and contraction of actomyosin. This hypothesis arose out of observations on the effects of digitalis on Na and K ion transport in normal and failing hearts.

Physiological Considerations

Even though we know considerable about the over-all energy metabolism of the normal and failing heart, little is known of the molecular events that underlie the other well-known physiological properties of the heart.

It has long been known that cardiac muscle displays certain peculiarities. There are: 1) its automaticity, 2) the existence of a refractory state, 3) the all or none response to stimuli of different strengths, and 4) the "treppe" phenomenon as an effect of previous excitation. These characteristics seem so incontrovertible that experiments demonstrating them have served as student laboratory exercises in all countries during the past half century. Their basic value in spurring physiologic investigations during the last fifty years should be recognized. They provided the impetus which impelled physiologists to search for similar characteristics in isolated muscle and nerve fibers, as soon as adequate instruments become available. Indeed, these supposed "peculiarities" of cardiac muscle are basic biological characteristics of all cells.

These properties referred to above are intimately associated with the electrical properties of the heart. Fortunately, something is known of the nature of the physicochemical events that underlie these phenomena, and it may be instructive to give an historical review of our knowledge of the subject.

By 1900, the successive contributions of Mattucci, Du Bois-Reymond, Herrmann, Bernstein, and others had already contributed a great deal of information concerning currents of rest and action. The majority of physiologists favored the view that currents derived from an uninjured and an injured surface reflect potential differences between the interior and exterior of muscle cells. Indeed, Samojloff in 1899, reported values of 60 - 80 MV which he estimated to represent 60 per cent of the actual potential differences. These values do not differ materially from that obtained today using far more elaborate and expensive equipment.

In 1902 Overton expressed the view that excitation of muscle involves exchange of Na and K ions, but was puzzled because no known physical process could be thought of which restored the natural intra and extracellular balance of K and Na. Overton's interpretations are generally accepted today.

Recent observations on the transmembrane flux of Na and K ions can, in a general way, account for the electrical properties of the heart during rest

and activity. Thus depolarization is believed to be the result of a sudden rapid inward movement of Na ions. On the other hand, recovery, or repolarization, occurs because of inactivation of the inward Na flux and an augmented outward movement of K ions. During the intervening periods of rest, the ionic gradients are restored by metabolic processes actively reabsorbing K and extruding Na. Since the two ions are exchanged, in this latter process, in equivalent amounts no net potential changes are observed. It is thought that the length of the refractory period is controlled by the availability of the inward Na current and the rate at which the outward K current restores membrane excitability to the resting level.

A propagated response only develops when the inward flux of Na exceeds a certain critical rate. This could be a physical interpretation of the all or none response as well as the phenomenon of threshold.

Drugs such as quinidine which lengthen the refractory period do so by slowing the rate of repolarization. According to the ionic hypothesis, this results from a depressive effect of quinidine on the augmented outward movement of K ions that occur during this phase of cardiac activity.

Even though the ionic hypothesis did not arise from biochemical considerations, it has proved most useful in interpreting in physical terms what the pharmacologist refers to as refractoriness, threshold, depolarization, etc.

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INTRACELLULAR RECORDING IN THE HEART

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Introduction

Ling and Gerard (1949) published the first study in which the ultra-microelectrode was employed in biological research. This investigation was a sequel to the work of Graham and Gerard (1947) in which frog sartorius muscle had been impaled with capillary electrodes of 2-5 microns tip diameter. The 1949 study further refined electrode preparation by decreasing tip diameter to less than one micron. These studies were largely responsible for introducing the technique of single cell recording to biological research.

The success of this type of electrical recording depends on the ability to penetrate with the electrode tip the membrane of a single cell, usually in a multicellular preparation. In order to preserve the integrity of the cell membrane, to be able to penetrate, and to avoid multicellular recording, the tip of the electrode necessarily must be very small. In practice, the tip diameter of a useful electrode should be 0.5 micron or less.

Electrodes are pulled from heated glass capillary tubing, usually of one mm. or less diameter. Various commercial electrode pullers are available, and some laboratories fashion spring-loaded or gravity-loaded pullers according to individual preference. The most direct, although not necessarily the best means of preparing electrodes is to pull them by hand over a microflame. With some practice it is possible to produce adequate numbers of uniformly drawn electrodes within a relatively short time. Various names have been given the glass capillary electrodes used in this technique. Because of the very fine tips, and to distinguish them from the tiny extracellular electrodes employed in neurophysiological research, and other areas, some term these ultramicro-electrodes. To others they are micropipettes, although this term usually connotes addition or withdrawal of intracellular material through the bore of the capillary.

Electrodes are filled with concentrated potassium chloride solution. While the concentration usually is expressed as 3 M, a convenient method is to use half-saturated solution of KCl. Filling is accomplished by boiling a group of electrodes in this solution for approximately one hour. Cooling and refrigeration results in completely filled electrodes. If boiling is accomplished under negative pressure (Kirk and Falk, 1957) filling time can be greatly reduced. Complete filling results in an electrode with a resistance of about 50 to 100 megohms. Incomplete filling produces very high resistance and the electrodes are not suitable for use. Abnormally large tip diameters bring about marked reduction in resistance. Most microelectrode circuits are equipped to check

electrode resistance. The resistance check is an approximate measure of filling and of tip diameter.

Recording of the Membrane Potential

The function of the microelectrode is to pierce the membrane of a cell and establish electrical connection between the interior and exterior of the cell. Therefore, an indifferent electrode must always be associated with the intracellular connection in order to complete the circuit.

The indifferent electrode may be placed anywhere in the chamber fluid in isolated tissue work or it may be in contact with the animal's body in studies involving intact animals. Probably it is best to have it as close to the intracellular electrode as possible as will be explained below. In the circuit is the recording assembly, essentially a refined voltmeter. In advance of the final DC amplifier - recorder is a cathode follower unit, or impedance converter necessary to match output with input impedance in order to increase quantitative fidelity of the recorder. It must be remembered that the combined output impedance of combined microelectrode and cell membrane may be in the neighborhood of about 100 megohms. This must be reduced before entering the input impedance, in order to avoid voltage loss in the final display.

The potentials recorded are those across the cell membrane. These are variably known as intracellular potentials, membrane potentials or transmembrane potentials. Recently Easton (1957) has suggested that a distinction should be made between intracellular and transmembrane potentials. His distinction is based on the contributory effect of adjacent fibers to the measured potential. Essentially, in Easton's view, the less the distance between microelectrode and indifferent electrode, the more nearly the recording represents the transmembrane potential of the particular cell impaled.

Origin and Characteristics of Membrane Potentials

Membrane potentials exist in all living cells. In nonexcitable tissues, the membrane potential is relatively stable during normal cell life. Various theories are associated with the origin of the membrane potential. On an ionic basis the most simple view (Hodgkin, 1951) is that the discrepancy between intra- and extracellular cations results in the generation of bioelectric potentials through a concentration cell effect. In support of this idea, the Nernst equation for potential difference across a semipermeable membrane may be applied within limits to biological cell membranes. However, it is apparent that metabolic work, through the mediation of active transport mechanisms (Hodgkin and Keynes, 1955) is required to maintain the separation of ions against thermodynamic gradients. Much remains to be learned in this area.

The stable membrane potentials existing in excitable cells are generally known as membrane resting potentials. Quantitatively these are of the order of 60-80 millivoots negative in nerve, skeletal muscle, and cardiac muscle. Lower values are found in smooth muscle. When the cell ceases to rest, i.e., upon

excitation the membrane action potential. The membrane resting potential represents a state of membrane polarization. Upon excitation the resting potential abruptly dissipates, producing a deflection on the recording instrument. Conventionally, the single-cell recording technique adjusts polarity of the leads such that an upstroke represents a positive going potential, while downstroke represents a negativity. With excitation an upstroke occurs representing loss of membrane polarity. This then is the depolarization limb of the membrane action potential. Particularly in nerve, skeletal muscle, and cardiac muscle, depolarization goes beyond the zero potential line and various degrees of "overshoot," or reversal of membrane potential, are displayed. The brief instant of depolarization is replaced by the more slowly developing repolarization, or recovery from the excitatory process.

Qualitatively, the membrane action potential is similar in all excitable tissues. Quantitatively, it will differ according to the source of tissue, environmental temperature, influence of chemical agents and other factors. In a recent monograph Weidmann (1956) illustrates the comparative appearance of membrane action potentials from several types of excitable cells. Resting and action potentials in all these examples show about the same voltage magnitude. Duration and configuration differ.

Intracellular Recording in the Heart

In spite of the delicate nature of the microelectrode, it is possible to record from the beating heart (in situ or in isolation) of different animal species. The ability to accomplish intracellular recording in moving tissues without traumatizing the preparation to immobilize it resulted from development by Woodbury and Brady (1956) of the "floating electrode." A length of fine (one mil) tungsten wire connecting glass capillary electrode shaft to electrode holder acts as a shock absorber and allows the electrode to "float" with the movements of the tissue.

When intracellular potentials are measured in intact animals it is clear that the membrane potentials bear only a temporal resemblance to the electrocardiogram, or to surface cardiac electrograms. It is interesting to compare the membrane potentials of the in situ frog heart (Woodbury and Brady, 1956) with the simultaneous electrocardiogram. Atrial depolarization occurs during the P wave. Repolarization comes to completion in the S-T segment. Ventricular depolarization begins in the QRS and is completed coincident with the T wave. Similar relationships in the mammal had already been described by Hoffman and Suckling (1952) in thoracotomized dogs. Further illustrations of intracellular potentials compared to the EGG are taken from unpublished work in this laboratory. In the rabbit heart it is possible to obtain potentials from the sinoatrial node in situ. Here the pacemaker potential precedes the P wave appreciably as it should if the heart beat originates in the area penetrated. Thus, intracellular recording from the heart can be correlated with the electrocardiogram, but at present, only in a temporal way. The challenge is to relate single cell activity with total cardiac function, in the parameters of both electrical and mechanical activity.

The *in situ* recording of intracellular potentials in heart is difficult. It is not surprising that most studies have been performed in isolated tissue preparations. Draper and Weidmann (1951) recorded from isolated Purkinje fibers of dog and kid hearts. Two microelectrodes were used and placed a slight distance apart in the same fiber. For the first time it was possible to accurately record conduction velocity, which was found to be 2.2 meters per second. In a subsequent paper (Weidmann, 1951) used the same technique to determine effects of current flow on the membrane potential. Among other findings, he was able to relate changes in membrane resistance to various phases of the action potential: resistance was decreased during the upstroke of the action potential and elevated during the plateau phase. A similar study (Weidmann, 1952) resulted in determination of some of the electrical constants of Purkinje fibers. For example, the resistance of the surface membrane was found to be 2 megohs per square centimeter and the membrane capacity 12 uF per square centimeter.

Burgen and Terroux (1953) and Hoffman and Suckling (1952) were the first to report the nature of atrial intracellular potentials. Burgen and Terroux found the active membrane potential of the isolated cat atrium to be small, compared with potentials obtained from ventricular preparations. Hoffman and Suckling observed a similar comparison in the intact dog atrium.

At Heidelberg, Trautwein and collaborators emphasized the simultaneous measurement of contractile tension and intracellular potentials. Trautwein and Dudel (1954) showed the effect of altered temperature on membrane action potential and contractile force in cat papillary muscle preparations. Decrease in temperature resulted in increased contraction strength and simultaneous broadening of the membrane action potential. Further studies by the same authors (Trautwein and Dudel, 1954) showed that increasing beat frequency first increased and then decreased contraction force; however, action potential duration decreased consistently with the rise in rate. The effect of increasing beat frequency also was studied by Hoffman and Suckling (1954) in dog papillary muscle, where again increased rate decreased the duration of the action potential. This effect appears to be even more noticeable in the intact dog atrium (Levy and West, 1957). In atrial fibrillation or flutter resulting only from rapid direct stimulation of the *in situ* atrium, atrial intracellular potentials may become extremely short in duration. Trautwein and Dudel (1954) also demonstrated in cat papillary preparations that oxygen lack decreased contraction force simultaneously with a shortening of membrane action potential duration.

Pacemaker Potentials

During isolated tissue studies involving Purkinje fibers, Coraboeuf and Weidmann (1954) and Trautwein and Federschmidt (1953) reported the presence of pacemaker potentials in preparations beating spontaneously. The pacemaker potential was characterized by slow diastolic depolarization, a phenomenon never seen in cells under the domination of a relatively remote source of impulse origin. Both groups studied temperature effects on Purkinje pacemaker preparations. Lowered temperature was shown to decrease the slope of diastolic depolarization (the prepotential) coincident with a decrease in spontaneous beat frequency. It was suggested that the rate of rise of the prepotential was positively correlated with spontaneous rate of beat.

The need to record intracellular potentials from a normal pacemaker site remained. Brady and Hecht (1954) explored the sinus venosus region of turtle hearts with the microelectrode. Pacemaker potentials were obtained in which the disstolic prepotential was characteristic. West (1955) reported the pacemaker activity of the sinoatrial node of isolated rabbit hearts at physiological temperature. Prepotential, retarded depolarization and ease of pacemaker migration were emphasized. Del Castillo and Katz (1955) investigated the effects of inhibitory nerve stimulation on the frog sinus venosus and Hutter and Trautwein (1956) reported the effects of vagal and sympathetic stimulation on frog and turtle sinus venosus. Almost simultaneously West, Falk and Cervoni (1956) described drug alteration of pacemaker potentials in the isolated rabbit heart.

Assuming that heart rate can be influenced by alteration of pacemaker cell membrane changes, one can postulate the nature of the change required to accelerate or retard the beat, considering the pacemaker prepotential as a local response, either the level of the critical firing point, or the rate of rise of the local response could influence rate. That is, if the prepotential slope remained constant, but the critical firing level were altered by a chronotropic drug, rate could be altered in accordance with the change in threshold. Or, if critical firing point remained constant, but slope of prepotential were altered by drug or hormone, rate alteration could result from this mechanism. As will be described, chronotropic drugs or neural influences may be shown to be associated with prepotential changes. Whether such changes are the only factors involved in rate alteration is not yet clear.

Membrane Changes and Contractions

It is tempting to explore the possible link between excitation and contraction in heart muscle. The microelectrode technique makes such a study likely in view of the ability to observe membrane changes in single cells. The isolated preparation may be suspended horizontally with one end secured to the arm of a sensitive strain gauge. Tension and electrical activity may be measured simultaneously on a multichannel recorder. One difficulty lies in the fact that contraction as usually measured is the result of multicellular participation, while the electrical activity observed represents a single cell. This is not a major problem if it can be assumed that the cell impaled is representative of all the cellular units participating in the total contraction.

As noted above, Trautwein and Dudel (1954) compared contraction and intracellular potentials of cat papillary muscle at different temperatures. At the same time action potential duration increased, chiefly due to progressive retardation of repolarization rate. Trautwein and Dudel denied a strict correlation between electrical and mechanical parameters because of divergence in the ratios of change between the two parameters. Webb and Hollander (1956) investigated the effect of substrate depletion on intracellular potentials and contraction in isolated rat atrium. After three hours in the absence of substrate, developed tension fell to about 12 per cent of control, action potential duration decreased to about 60 per cent of control, but action potential amplitude remained essentially unchanged. Upon the introduction of pyruvate or glucose into the nutrient solution the effects of substrate depletion were quickly

reversed, although incompletely. Qualitatively similar findings were reported by Trautwein and Dudel (1956) when cat papillary muscle was subjected to oxygen deficiency.

Marked transient increases in contractile tension can be observed in isolation following extrasystoles, short periods of rapid electrical stimulation, or periods of quiescence interrupting a steady basal rate. Postextrasystolic potentiation of contraction in cat papillary muscle was studied by Hoffman, Bindler, and Suckling (1956) with the aid of intracellular recording and isometric measurement of contractile force. Although experimental tension increased markedly, action potential configuration was altered insignificantly in the muscle used. In contrast, West (1957) has observed delayed terminal repolarization with poststimulation potentiation of contraction in ventricular strips isolated from rabbits. Cervoni and West (1956) found a correlation between membrane repolarization and contractile force in isolated rabbit atrium during poststimulation potentiation and postquiescence potentiation of contraction. In their preparation the degree of contraction increase during maximum potentiation was proportional to retardation of terminal repolarization, or to duration of the action potential.

A recent communication of Brady (1957) states, "The close correlation between duration of action potential and maximum contractile tension suggests that the fiber membrane potential determines the duration of the active contractile state." In general, it appears that membrane action potential duration and contraction strength are directly proportional. However, there appear to be exceptions. As Trautwein and Dudel (1954) have shown, increasing beat frequency in cat papillary preparations leads to a bidirectional curve for isometric tension change, but an unidirectional curve for changes in action potential duration.

The Effects of Chemical Agents on Intracellular Potentials Acetylcholine

The effect of cholinergic agents on cardiac membrane potentials has received considerable attention. Burgen and Terroux (1953b) described the acceleration of repolarization induced by acetylcholine and carbamylcholine in the cat atrium. Hyperpolarization also resulted, predominantly from the latter drug. Hoffman and Suckling (1953) studied the effects of vagal stimulation and of acetylcholine in the intact dog heart and the effect of acetylcholine in isolated atria and papillary muscles of the dog. Vagal stimulation and acetylcholine administration had the effect of profoundly shortening artrial cell action potential duration through marked acceleration of repolarization. This effect was completely blocked by atropine. In contrast, ventricular potentials were unchanged following either vagal stimulation or acetylcholine infusion, whether observed in the intact dog or in the isolated preparation. Similar findings have resulted from the unpublished experiments of Levy and West (1957), in which acetylcholine also was applied locally at the site of electrodeimpalement. In the dog, at least, the ventricular cell membrane is greatly different from the atrial cell membrane in its responsiveness to cholinergic influence.

In the pacemaker fibers of the sinus venosus of the turtle, Hutter and Trautwein (1956) observed vagal stimulation to reduce prepotential slope,

inhibit the development of the pacemaker action potential and to cause apparent hyperpolarization. West, Falk and Cervoni (1956) found that the administration of acetylcholine at the site of electrode impalement in the sinoatrial node of isolated rabbit preparations also reduced prepotential slope and reduced the height of the pacemaker action potential. These effects occurred concomitantly with a decrease in spontaneous rate. In the mammalian experiments there was no noticeable increase in membrane polarization.

There is some evidence for the mechanism of the acetylcholine effect in terms of membrane permeability to potassium. Trautwein, Kuffler, and Edwards (1956) have shown in frog auricles that acetylcholine increases muscle membrane conductance. Harris and Hutter (1956) studied movements of radioactive potassium in frog sinus venosus. Both addition of acetylcholine and vagal stimulation increased potassium permeability, regardless of direction of potassium movement. It is possible that the accelerated repolarization seen in intracellular potentials from atrial sites is the electrical representation of increased outward movement of potassium ions. Harris and Hutter also noted that the acetylcholine effect was most marked in the sinus venosus, compared with auricular sites. The inference could be drawn that pacemaker automaticity is involved with optimal membrane permeability to potassium.

Epinephrine

Relatively little information exists regarding epinephrine effects on cardiac membrane potentials. In isolated rat atria, Webb and Hollander (1956) observed epinephrine to have effects generally opposite to those resulting from acetylcholine. The increase in contraction force was associated with a slowing of repolarization rate and with depression of magnitude both of active and resting membrane potentials.

Adrenergic effects are more obvious in pacemaker sites. Hutter and Trautwein (1956) found that sympathetic stimulation increased prepotential slope in the frog sinus venosus. At the same time, in contrast to the results of Webb and Hollander, action potential amplitude increased, although there was no change in resting potential level.

The sinoatrial node of isolated rabbit atrium responds similarly upon the administration of epinephrine (West, Falk and Cervoni, 1956). Prepotential slope is increased coincident with the increase in spontaneous rate.

Quinidine

In view of the well-known ability of quinidine to prolong refractory period in the heart, it is reasonable to suspect that it may delay the repolarization process, among other possible actions. Retardation of repolarization in cells of isolated rabbit atrium results from quinidine administration (West, 1955). Johnson (1956) studied the effects of quinidine, procaine amide and pyrilamine on resting and action potentials in the guinea pig ventricles. Reduction in depolarization rate, loss of overshoot and some delay in membrane repolarization

were seen. Quinidine and like drugs exert similar effects in isolated rabbit atrium (Levy and West, 1957). These effects develop relatively slowly and are difficultly reversible by washing. Changes in membrane action potential configuration are paralleled by increased refractory period, elevated threshold of excitability, increased conduction time and slowing of spontaneous rate. Unpublished observations of Levy and West (1957) indicate that atrium and ventricle of the intact dog and the intact rabbit respond qualitatively similar to the isolated rabbit atrium in response to quinidine and like drugs.

Quinidine in general acts in the opposite sense to acetylcholine. Arrhymias induced as a result of combined acetylcholine and brief, rapid stimulation of the isolated atrium (West, Turner and Loomis, 1954) are reversed or prevented by suitable concentrations of quinidine. The changes in membrane action potential exerted by quinidine suggest that it affects ion movements in a manner contrary to the effect of acetylcholine. That is, if acetylcholine increases membrane conductance in heart through increasing membrane permeability to potassium, quinidine and similar drugs might be expected to reduce potassium permeability and to increase membrane resistance. Holland (1957) gave evidence that quinidine does indeed decrease the outward flux of potassium ions in isolated rabbit atrium, and further suggests that this effect is due to the blockade of intracellularly released acetylcholine.

Cardiac Glycosides

Relatively little work has been undertaken to determine the effect of digitalis on membrane potentials in heart. Woodbury and Hecht (1952) found that digitoxic first lengthened, then shortened the duration of membrane action potentials in frog ventricles. Membrane resting potential was not affected, and contraction force was not affected significantly until extreme shortening of action potential duration became apparent. Stutz et al (1954) investigated the effect of cedilanid on extracted and nonextracted heart muscle strips from dogs. Mechanical activity and intracellular potentials were measured. Although the glycoside produced no significant change in mechanical properties, cedilanid (0.1 mg. injected I.M. daily for twelve days prior to sacrifice) evoked marked shortening of action potential duration and loss of overshoot. These results were essentially similar to those of Woodbury and Hecht (1952), obtained in amphibian preparations. The phenomenon of extreme shortening of action potential duration with depression of contractile force also was seen by West and Levy (1957) in a study comparing the effect of ouabain on the sinus node and nonsinus cells of isolated rabbit atrium. The latter authors deliberately used "toxic" concentrations of the drug in order to induce atrial asystole.

Conclusions

The intracellular recording technique represents an advance in instrumentation analagous to the development of the electron microscope. It enables the investigator to "see" much more closely. The result of the closer view is to refine description, not explanation. The method opens new vistas for the electrobiologist. It helps piece together fragments of information from other sources.

It has definite advantages and just as definite limitations. Used widely, within its limitations, intracellular recording will contribute greatly to the physiology and pharmacology of excitable tissues.

LABORATORY APPROACHES: VENTRICULAR PERFORMANCE AND ITS MEASUREMENTS

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Much of our current knowledge of cardiac function is based on work done in the heart-lung preparation or in anesthetized, thoracotomized dogs. Some ten years ago I became convinced that the results of many experiments are applicable only to particular experimental conditions, and do not necessarily apply to an intact animal under normal control mechanisms. My only message actually consists of indicating to you some methods that have been worked by a research team, consisting of physiologists, surgeons, electronic engineers, and technicians, for studying the manner in which the heart performs in the intact dog. As time goes on such methods may become more universally available for studies of pharmacological agents as well as normal control mechanisms.

Our initial attempt was made to study cardiac function in dogs by means of X-ray movies. This consists of taking motion pictures of fluoroscopic images while contrast medium is going through the heart and lungs. We obtained the films and then studied changes in size and shape of the individual cardiac chambers. When the cardiac chambers are filled with a radio opaque medium one cannot see where any one spot on the heart is moving. Therefore, we developed techniques for implanting little metal markers on both side walls of the heart in order to study the movement. We can synthesize then the changes in the size and shape of the heart as developed from the movements of individual points. Subsequent to this time we have utilized four different means of measuring continuously the changes in heart dimensions by various electronic techniques and it is to these that I shall devote most of my attention. (Motion picture)

This motion picture is a summary of the various techniques that we have used in the past. The pumping action of the heart is indicated by a slow motion picture of diodrast going into a heart on which have been mounted little metal markers on the inside and outside of the heart walls. By combining from these motion pictures the changes in size and shape of these chambers one can synthesize the action of the individual byocardial walls. Notice how incompletely the ventricles empty.

The next approach was to produce a gauge which was installed within the left ventricular cavity. It consists of a coil with a stylus inside. By changes in the inductance in the coil it is possible to measure very accurately the position of the stylus in that coil. With the heart functioning, any movements of these walls toward one another will be recorded as a change in diameter as measured by the gauge. The dogs were permitted to recover, the wires from the coil were let out through the back and recordings could then be taken at any time thereafter. In one animal the gauge continued to respond accurately for twenty-six days after it was installed.

Delicate rubber tubes filled with mercury were also installed in the heart. One encircled the left ventricle and another was mounted lengthwise on the left ventricle. With changes in ventricular circumference, the diameter of the mercury column was reduced and the electrical resistance increased. Within the mechanical limits of the gauge, resistance change was proportional to circumference change.

The animals were also prepared so that they could be studied while exercising. Our initial attempts were done running up and down the halls in front of portable recorders. We studied not only exercise, but also many common activities such as eating, sleeping and sudden noises, changes in position, etc.

The next technique which we employed was one that is a modification of sonar. The distance between two points can be measured if the time required for a sound wave to go from a transmitter crystal to a receiver crystal and the speed of sound and transmission is known. With two barium tetinate crystals mounted on opposite sides of the left ventricle the time required for sound to travel from the transmitter crystal to the receiver crystal is an indication of left ventricular diameter. A pressure gauge simultaneously records continuously the effective left ventricular pressure. Now from these two variables, by the means of electronic computors, it is possible to derive additional information about ventricular performance. The upper trace is a continuous measure of heart rate by a condensor discharge technique. The distance that this trace falls is an indication of heart rate.

By an electronic differentiating circuit we can measure continuously the slope of the circumference record. The resulting parameter then represents the rate of change of circumference. The distance that the deflection moves from the base line is an indication of the slope on each part of the curve. By means of a multiplying circuit we can continuously multiply rate of change of dimension by the effective ventricular pressure and get a measure of power. The power record indicates the rate of doing work by that sample of myocardium that is under the gauges. By means of an integrating circuit we can measure only the area of the positive deflection in the form of a series of steps. The amplitude of the step indicates the size of the area and determines the relative magnitude of the work being done. By triggering this back to the base line at regular intervals the total height attained during each time interval represents the cumulative work per unit of time.

If a dog eats a plate of food, the cardiac response to that particular activity can be noted. The heart rate increases rapidly. It attains a very high level in a matter of only a few beats. At the same time the systolic ventricular pressure rises, the diastolic pressure rises, falls and rises again and there is the sudden change in the left ventricular diameter. The cumulative work (the amount of work per unit of time) increases and then falls off as the heart rate changes. The systolic pressure also fluctuates. The heart becomes small during this activity, partly because heart rate increases. Our dogs are exercised now on a treadmill because it is easier to control the animals. Some of these dogs have done this so many times that they will run without being attended. We now are recording eight different variables on two different recorders, using all of the electronic apparatus. (End of motion picture)

The result of infusing different autonomic hormones can be described. Epinephrine was injected intravenously at the rate of 0.4 gamma per kilogram per minute. Left ventricular pressure increased as did circumference, myocardial power, and cumulative work. Levarterenol at the same dosage level gives a very similar pattern of response, but there are some differences. One difference is that levarterenol in this particular animal caused a greater slowing of the heart than did epinephrine. When acetylcholine was infused the ventricular pressure fell rather markedly and remained generally depressed. But gradually pressure recovered over this long period of infusion. The circumference change followed a similar pattern. Acetylcholine caused a reduction in the cumulative work in spite of increased heart rate. This indicates stroke work materially reduced as was the myocardial power under the influence of acetylcholine.

When levarterenol was administered to an unanesthesized dog there was very little change in left ventricular pressure. The lack of response was ascribed to compensatory mechanisms in the animal itself. We administered tetraethyl ammonium chloride at this point during the norepinephrine infusion. Immediately after the tetraethyl ammonium chloride began to act a large increase in ventricular pressure was observed, accompanied by a change in power and a change in cumulative work. This indicated that during this phase the normal response to the levarterenol had been actually diminished by compensatory mechanisms which could be blocked by tetraethyl ammonia chloride.

The effects of epinephrine and levarterenol do not resemble the cardiovascular effects of exercise. First it must be realized that variation in the exercise response can occur in the same animal on the same day under constant experimental conditions. This is an indication I believe of the activity of neural reflex phenomena which are influencing the performance of the heart, removing certain facets of the control from the mechanical phase into neural controlling mechanisms. For example, if an animal is placed on the treadmill, changes can be obtained in these various parameters of ventricular performance which look very much like those seen at the onset of exercise even though the dog was only placed in position to exercise. It was of interest to observe the extent to which the administration of epinephrine or levarterenol would reproduce the response to exercise. However, because of the rather intense bradycardia which accompanies epinephrine and levarterenol, it was impossible to reproduce the exercise response by the simple administration of infusion of either drug. It implies that neither substance is the primary or predominant mechanism for changing cardiac function during exercise, at least unaided. A combination of levarterenol and isoproterenol resulted in a response which more closely resembled that of exercise, but as yet isoproterenol is not ordinarily recognized as a naturally occurring catecholamine in the animal in normal circumstances.

In a series of experiments, atrial electrodes were sutured near the sinus node to the right atrium. Thus the heart rate can be controlled through this artificial pacemaker. The heart rate was changed through the steps of 90, 120, 150, 180, 210. The responses of left ventricular pressure, left ventricular diameter, cumulative work and other parameters were observed. As the heart rate increased, the diastolic size diminished as did the stroke size. This is not surprising. When the stimulator was turned off abruptly, a marked change in ventricular pressure accompanied the cessation of controlled heart rate. Since

we know of no neural connections which are likely to be stimulating on the atrium in this position that will effect left ventricular pressure, it would appear that electrical stimulation of the left atrium is not entirely innocuous and we may be stimulating afferent fibres in the right atrium.

A series of dogs was prepared with stimulating electrodes on the right atrium which served as an artificial pacemaker. The electrical signal of the rising limb of ventricular pressure was allowed to produce clicks on a tape recorder. When the dog was exercised the exact sequence of changes in heart rate was recorded on tape during the exercise response. This response was then played back into the stimulating electrodes on the dog's heart. When the changes in heart rate, duplicating the dog's exercise response, was combined with administration of .004 micromoles per kilograms per minute of epinephrine, a response not too different from the original exercise response was observed. This phenomenon also occurs using levarterenol. However, approaching the exercise response by this means is effective only when the predominant change in the ventricular performance is a tachycardia. When the principal change in the cardiac performance is a change in stroke volume rather than heart rate, then we can no longer so exactly duplicate the exercise response by combining the dog's own heart rate control with autonomic hormones.

INTERPRETATION OF DRUG EFFECTS ON THE HEART: CLINICAL APPROACHES

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Investigation of effects of drugs upon heart function in humans has increased in recent years for several reasons. Progress in medical and particularly surgical treatment of congenital and acquired cardio-vascular diseases has been both a cause and result of increasing interest in basic physiological and pharmacological research. New techniques have originated for detection and quantitation of the physiological abnormalities found in such diseases. Although use of many of these techniques has been largely for assessment of given abnormalities in relation to normals, or comparative evaluations before and after surgery, there is also increasing interest in assessment of effects of drugs.

There are problems in drug evaluation in humans not encountered in animal experiments. Obviously the welfare of the subject must remain a primary consideration and this limits application of techniques involving risk. Apprehension, motivation, and anxiety may influence the most careful investigations. Attitudes of both subjects and examiner may materially influence results. In spite of the invaluable aid of animal experiments and limitations of experimental approaches in human subjects, adequate investigation of drug effects in humans is, in the last analysis, the only method to properly evaluate the benefits of such drugs in management of patients. To quote Claude Bernard, the father of experimental medicine (1), "Experiments made on man are always the most decisive."

The purpose of this discussion is to mention some of the methods of assessing cardiac function in man which have been either developed or applied in the last decade. Use and interpretation of some of these techniques in the study of drug effects will be mentioned. Obviously only certain aspects of this broad field can be covered. Selection has been made to illustrate the range of complexity of such techniques in present-day use.

Evaluation of Symptoms: Angina Pectoris

Evaluation of symptoms, seemingly simple but actually fraught with many difficulties, has been used extensively to investigate drug effects in the treatment of angina pectoris. By definition angina pectoris is sensation of a type of chest pain, and is therefore entirely subjective. Such pain is usually thought associated with inadequate supply of oxygen to the myocardium. Variations in frequency and severity of this pain often occur. Alteration of sensory perception due to changes in motivation, activity or emotional stresses, as well as presumed variation in underlying coronary artery disease, are thought responsible for the variability of pain noted. Because of such factors relationship of pain perception to the underlying organic disease may be variable in some patients.

A variety of results has been obtained in clinical evaluation of drugs proposed for treatment of this disease. Some of the discrepancies can be explained by differences in methods of evaluation and criteria of improvement. For example, Kory and co-workers (2) evaluated khellin, heparin and peritrate, based upon frequency and severity of pain as reported by the patient and electrocardiographic changes during Levy's anoxemia test. The latter employs inhalation of 10 per cent oxygen for 20 minutes. Patients were given placebo for two weeks and then drug for two weeks with anoxemia tests before and after each period. Variations in the severity of pain, related to physician-patient relationship and unrelated to specific therapy, were abundant. In the use of khellin four of six patients had improvement in both subjective and/or objective criteria during placebo administration only. One patient had disappearance of angina decubitus on the second day of drug, but no change in the anoxemia test. Although reduction in pain continued, the drug was never stopped or substituted to further evaluate its effects. Of six patients tested with peritrate none showed reversal of anoxemia tests but two had striking improvement in pain. Again such effects were not evaluated later by drug substitution. Yet results of this limited study are quoted in a recent advertisement in a medical publication as follows: "New studies continue to confirm the effectiveness of this long-acting coronary vasodilator. 'Impressive and sustained improvement' is observed in patients on peritrate therapy." However, the sentence in the summary from which this quote is made states "Peritrate provided impressive and sustained subjective improvement in two of six patients, but failed to alter the anoxemia test in any way."

A recent study of anti-anginal agents reported by Cole, Kay, and Griffiths (3) employed both double blind technique and multiple control periods employing no drug, as well as placebo. Evaluation was made by relation of frequency of pain to the different regimes. Reduction of pain occurred during the early weeks of study without regard to the drug used in 14 of 24 selected patients. Control periods late in the course of study often showed reduction of pain on comparison with initial control periods. Such improvement is most likely not a pharmacological effect but indicates the limitations of studies, such as that first mentioned, not permitting repeated periods of control observations. Specific effect of a drug (peritrate) upon the incidence of pain was noted in only one of Cole's 24 patients. Metamine, calcium theophyllinate (calphyllin) and chlorpromazine were without observed beneficial effects. Variations occurred due to illness, emotional strain, progression of disease, or unknown factors.

Because of such difficulties in evaluation of the subjective sensation of angina pectoris, Russek and co-workers have utilized response to Master's two-step test as an objective method of evaluating coronary insufficiency, as opposed to angina pectoris. In this test (4) the patient makes a predetermined standard number of trips up and down two nine-inch steps with comparison of the electrocardiogram before and after exercise. Standards for abnormal ST and T wave changes have been established. On screening some 3,000 patients over a four-year period Russek found 52 persons who exhibited a relatively constant abnormal electrocardiographic response to a given amount of such exercise. Multiple test of the newer anti-anginal drugs indicated favorable alteration of the electrocardiographic response in 14 of 21 patients following peritrate (5). No improvement was noted using paveril, metamine or nitroglyn.

Conclusions reached from these and other studies of effects of anti-anginal drugs in angina pectoris are suggested as follows:

1) Such studies are difficult to interpret because of numerous nonpharmacological factors effecting anginal pain. Some of these factors can be obviated by comparison of drug and placebo through double blind technique and use of multiple test and control periods.

2) There is considerable doubt as to significant reduction of pain of angina pectoris by any pharmacological action of the so-called long-acting coronary vasodilators in all but perhaps a small minority of patients studied.

3) In some patients with angina pectoris, peritrate may reduce the abnormal electrocardiographic responses to exercise.

Evaluation of Heart Function During Exercise

Various types of exercise tests have been employed to better evaluate disability in cardiovascular disease. Such objective tests supplement but do not replace the primarily subjective interpretations of patient and physician in evaluation of disability by the usual clinical history. Exercise tests provide an opportunity to quantitate parameters of function during and after exercise, to the extent that motivation is appropriate, anxiety minimized and noncardiac causes of disability eliminated. Effects of drugs on cardiac function in man during exercise can also be evaluated.

Master's step test (4), previously mentioned, is an example of such a test. Although originating as a study of physiological adaptation to exercise, this test has since been used most widely as a diagnostic test for coronary insufficiency, based upon changes in the electrocardiogram observed after exercise. Its use in the evaluation of anti-anginal drugs has been mentioned.

An exercise test employing walking on a motor-driven treadmill has been developed and used extensively by Bruce (6). Grade of 10 per cent and speed of 1.7 miles per hour are used. Exercise is continued for ten minutes (arbitrary) or to tolerance if shorter. Observations made during each minute, before, during, and after exercise, are: blood pressure, expired oxygen content, and recording from a precordial electrocardiographic lead. In addition note is made of symptoms experienced by the patients or abnormal signs apparent to the physician. Endurance and symptoms experienced constitute the most simple appraisal of tolerance for this form of exercise. A quantitative measure of performance termed "physical fitness index" (PFI) has been utilized. It is derived from endurance, average respiratory efficiency during exercise and total heart rate during the first three minutes of recovery. Respiratory efficiency is extraction of oxygen from room air expressed in volumes per cent. Thus PFI = $\frac{\text{endurance x resp. eff.}}{\text{3 min. recovery rate}}$ x 100. Since cardiac disease tends to reduce both endurance and respiratory efficiency and increase recovery heart rate, the derived index is a more sensitive measure of performance than any one of the single variables. Other parameters have been

measured, such as oxygen consumption, ventilation, respiratory rate, oxygen debt, and exercise heart rate. Patients and normal control subjects were best separated statistically by the derived index. Normal individuals complete the full ten-minute period of exercise without symptoms and with PFI scores usually above 13.

The use of this common form of easily performed exercise eliminates skill, minimizes anxiety, and equalizes variations in body weight. Results are highly reproducible. When used as a diagnostic test for coronary insufficiency this test offers the advantage of electrocardiography during as well as after exercise (in contrast to Master's test), in addition to the other observations of cardiac function. The test is safe, even in severely disabled patients, in part due to observations of the parameters mentioned during exercise. Hypotension, tachycardia or electrocardiographic changes (particularly evidence of ventricular irritability) observed during exercise may necessitate stopping the test, even in the absence of severe symptoms, before more marked changes occur. Disadvantages are the influences of inappropriate motivation, anxiety, and noncardiac causes of disability, factors important in all forms of exercise testing. The physician's time and expense of equipment are likewise significant.

As one would expect, in dealing with groups of patients there is good correlation between this measure of exercise tolerance and disability as expressed by functional classification of the New York Heart Association. This definition of functional capacity is based upon ease of production of symptoms during ordinary activity, as described by the patient and interpreted by the physician. In individual patients, however, discrepancy in these two criteria of disability is occasionally observed. Such discrepancies are due in large part to variation in "ordinary activity" levels from patient to patient, inability to obtain accurate history of symptoms, or abnormal attitudes of patients toward disease.

Although used primarily for evaluation of disability, this test has been used to detect changes induced by drugs. For example, studies of a 35-year-old male with aortic stenosis and normal sinus rhythm are shown. Systolic gradient of 80 mm. Hg. from left ventricle to brachial artery indicated very significant aortic obstruction. Exercise tests were done before and after oral digitalis therapy over an interval of ten days. Although able to complete the full exercise period both times, symptoms were less on the second test. Respiratory efficiency during exercise improved only slightly, being normal initially. Most impressive was the decline in three-minute recovery heart rate from 346 to 277. The PFI score accordingly rose from 15.0 to 19.9. Heart rate during exercise rose abnormally to 160 on the first test, but was normal (maximum 123) on the second test. In spite of the improvement in heart rate, systolic blood pressure during exercise remained low (although within normal limits) on both tests, a common finding in patients with obstruction of either aortic or mitral valves. It is quite possible that factors other than digitalis therapy alone were responsible for some of these observed changes in view of the interval between tests, although there were no changes in this man's clinical findings.

Patients have been observed in a similar manner in treatment of atrial fibrillation with quinidine. Results obtained in a 35-year-old female, who previously underwent commissurotomy for mitral stenosis, are shown before and after conversion to normal sinus rhythm with quinidine. Endurance and symptoms

remained essentially normal. Respiratory efficiency and recovery heart rate both increased following conversion, resulting in no change in over-all index. However, exercise tachycardia was excessive with atrial fibrillation, in spite of well-controlled resting and recovery rates, and decreased following conversion.

As a last example of the use of this type of examination for evaluation of drugs, results are shown before and after acute lowering of blood pressure with intravenous protoveratrine in a patient with essential hypertension. Reduction in blood pressure, heart rate, and respiratory rate, well known in humans at rest, were also observed during exercise. Blood pressure decreased from 270/160 to 170/105, heart rate from 140 to 105 and respiratory rate from 25 to 20.

Measurement of Cardiac Output: Ganglionic Blocking Drugs

Accurate techniques for measurement of rate of blood pumped by the human heart, or cardiac output, have been a necessity for clarification of heart function in health and disease. Two basic techniques are generally accepted today. The first utilizes venous injection of a suitable indicator substance which can be quantitatively identified in the arterial circulation. A plot of the resultant arterial concentration against time is then possible. Such time-concentration curves show an initial peak of primary circulation and subsequent minor fluctuations from recirculation in the arterial system. The downslope of the primary circulation can be assumed to be an expotential function of time. Thus re-plot of this downslope on a logarithmic scale and extrapolation of the resultant straight line define the portion of the primary curve obscured by recirculation. Cardiac output is then a function of the area under the primary curves expressed by the Stewart-Hamilton (7,8) formula: $F = I/A$, where F is flow in cc/second, I is mg. of indicator injected, and A is area under the primary curve in mg.-second/cc. As expected this indicates that the greater the dilution of a given amount of indicator, the greater the rate of flow must be.

This principle has been used in humans since 1928 (8), utilizing arterial blood sampling over continuous intervals. Analysis of indicator concentration in each sample allows estimation of a continuous time-concentration curve. Recent clinical application of oximetry now permits a continuous recording of arterial concentration in the ear lobe following peripheral or central venous injection (9). Direct arterial sampling is thus obviated. Evans blue, or other indicator dyes, are used for this purpose. Similar time-concentration curves can be obtained with suitably placed counters or arterial sampling following injections of small amounts of radioactive substances.

The second general method of measurement of cardiac output requires determination of oxygen consumption and arteriovenous oxygen difference during steady state. Flow is then equal to oxygen consumption divided by A-V difference (Fick principle). This necessitates a mixed venous, as well as arterial, blood sample. Agreement between these two basic methods is good. Use of indicator techniques allows fairly rapid and repeated determinations of output, but requires

considerable equipment and standardization. Use of the Fick principle is limited primarily by the necessity of cardiac catheterization for determination of mixed venous oxygen content.

Determinations of cardiac output have been of considerable value in determining mechanism of action of the ganglionic-blocking drugs in humans with high blood pressure. Although these drugs (hexamethonium, pentolinium, mecamylamine) were found to be potent hypotensive agents, and have proven valuable in treatment of some patients with hypertension, mechanism of pressure reduction was not known. It was initially hoped, and perhaps assumed, that the abnormal increase in peripheral vascular resistance present in hypertension was reduced through blockade of arterial vasoconstrictor impulses mediated by the sympathetic ganglia.

Acute effects of pentolinium in ten patients with hypertension before and one hour after intravenous administration have been reported by Crosley and coworkers (10). Cardiac output was determined in the supine position by cardiac catheterization and use of the Fick principle. Mean systemic pressure decreased 16 per cent. However, cardiac index also decreased 20 per cent. As a result systemic vascular resistance, proportional to the ratio of pressure to flow, was unchanged. Similar changes occurred in pulmonary artery pressure and resistance, right ventricular end-diastolic and right atrial pressures.

Chronic as well as acute effects of pentolinium in patients with hypertension were studied by Smith and Hoobler (11). Radioactive iodinated serum albumin was injected intravenously and counted via arterial sampling. Studies were done in the sitting position. Cardiac index decreased in all patients in both acute and chronic studies. Acute studies in five patients showed mean decrease of 37 per cent in both mean systemic pressure and cardiac index, with no change in peripheral resistance. Chronic studies in six patients done six to 128 days after onset of oral treatment showed similar results with mean pressure decreasing 24 per cent, cardiac index 25 per cent, and peripheral resistance increasing 5 per cent. Peripheral resistance was decreased slightly in only two of the acute studies and one of the chronic studies. In addition one patient who had been on therapy for one year was re-studied before and after cessation of treatment, when pressure returned to pre-treatment levels. Although pressure increased 17 per cent, cardiac index rose 44 per cent, and resistance decreased 15 per cent.

Other observations of results of this form of drug therapy are important in understanding their effects in humans. Decrease in right heart filling pressures were noted in the acute studies of Crosley (10). Precipitous decreases in blood pressure may occur in the erect position, occasionally resulting in syncope. However, immersion in water, in spite of the position, eliminates such postural hypotension (12). These and other observations suggest that a major action of these drugs is, directly or indirectly, on the venous, and not arterial, circulation. This may well be through blockade of venoconstrictor impulses. Thus reduction of venous return results in decrease in cardiac output, especially in upright posture when gravitational forces are more pronounced.

Such direct study of effects of these drugs in man have done much to clarify their mode of action, as well as to more clearly define the dynamic role of

venous constriction in normal physiological processes. It appears that the major effect of these drugs is not on the presumed primary abnormality in hypertension, namely increased arteriolar resistance. Nevertheless, the decrease in cardiac work resulting from reduction of both flow and pressure offers ample explanation for the proven effectiveness of these drugs observed on a clinical level. Clearer understanding of their mode of action should stimulate interest in search of suitable drugs with primary action on the arteriolar bed.

Coronary Sinus Catheterization: Digitalis

Considerable data has accumulated describing pharmacological effects of digitalis since the first systematic observations of Withering in 1785 (13). Improvement in cardiac output is noted both clinically and in the laboratory (14) following use of this group of drugs in many patients with congestive heart failure. However, possible effects of digitalis on myocardial metabolism, the underlying source of energy for cardiac work, have not been well defined in the past. Experiments utilizing tissue slices, heart-lung preparations and tissue homogenates have not yielded consistent results (15). Further comprehension of the effects of digitalis upon metabolism of the heart in persons with congestive heart failure has resulted from studies employing coronary sinus catheterization. In such studies cardiac catheterization is initiated in the usual way by inserting a catheter into the venous circulation. By suitable manipulation the catheter may frequently be passed into the coronary sinus, the vein draining most of the left ventricle and emptying into the right atrium. Myocardial extraction of a given substrate is measured by comparison of samples obtained from the catheter and a peripheral artery. Coronary blood flow can be estimated by the nitrous oxide method.

Such studies done before and after acute intravenous administration of lanatoside-C have been reported by Bing and co-workers (15). Eleven patients with heart disease were studied, including four with congestive heart failure. No significant changes were found in extraction of oxygen, glucose, pyruvate, lactate, fatty acids, ketone bodies or amino acids. Previous studies had shown no increase in coronary blood flow (16). Thus these findings indicated failure of lanatoside-C to produce significant changes in myocardial utilization of either available oxygen or metabolic sources of energy. This suggests the improvement noted in work performance of the failing human heart after digitalis is due to increase in energy liberation rather than energy consumption, or increased efficiency of energy conversion. Presumably this is through direct action on the contractile proteins of the heart muscle, as has been demonstrated in some studies of effects of digitalis on contraction of actomyosin threads (15).

Summary

In summary some of the presently used means of assessing cardiac function in humans have been mentioned, ranging in complexity of examination from evaluation of symptoms to coronary sinus catheterization. Mention has been made of the use of these methods for evaluation of effects of anti-anginal, ganglionic-blocking, and digitalis drugs. Many other techniques presently used, and other

important aspects of heart diseases and their corresponding drugs have not been mentioned. Continued investigation of effects of drugs on function of the human heart is both a natural outgrowth of past successes and a prerequisite for the most intelligent use of such agents in the management of patients with heart disease.

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WEDNESDAY AFTERNOON DISCUSSION SESSION

T. C. West, Chairman

Dr. West: Dr. Logan, will you elaborate on the Personal Fitness Index (PFI) in terms of the elements of the formula, the significance and its relationship to the rehabilitation program currently underway in Seattle?

Dr. Logan: It's a laboratory test, and I'll put no more faith in it than in any other laboratory test. It must be evaluated carefully in light of the patients one deals with. In general, we find that if we question a patient very carefully about his disability we usually can predict the type of performance expected in the test. The test is particularly indicated in certain patients with bizarre attitudes toward their disease--who describe symptoms unrelated to heart disease. In this type of individual we feel that the test is preferable in evaluation of their cardiac disability. The test has been used in Seattle as part of a rehabilitation effort to better understand how disabled certain people are and what type of occupation or trade they could best pursue. In addition we've been particularly interested in using it as an objective measurement of cardiac performance before and after various types of cardiac surgery. This helps eliminate the many subjective elements that enter into both the patient's and the physician's appraisal of improvement following surgery.

Dr. West: As I recall, some individuals have been treated by the test rather than by pharmacologic intervention, and have shown improvement apparently related to assurance gained by the patient from the objective results of the test.

Dr. Logan: Yes. Sometimes patients find that they have done surprisingly well on the test and will change their attitude toward their disease.

Question: Will you compare cardiac output determination by the Fick principle with that of the dye dilution method?

Dr. Logan: I think dilution methods would be superior when one wants a rather rapid measure in a situation that may not be too stable. The Fick principle in theory depends on the presence of a steady state, so that the changes in oxygen consumption and the A-V difference that occur are averaged out and may not be very applicable to abrupt changes. Other types of tests have been proposed, all the way from analysis of peripheral arterial pressure curves to the use of the ballistocardiogram. These simpler techniques are inaccurate in many situations, but may be applicable where one wants multiple, simply-determined observations for relative changes.

Dr. West: This morning Dr. Holland talked about the changes in intracellular electrolytes during arrhythmias in isolated preparations and during control of such arrhythmias by the so-called antifibrillatory drugs. Can this be related to clinical situations in terms of serum or tissue electrolytes?

Dr. Holland: It is known clinically that people become more sensitive to digitalis in the presence of hypopotassemia. The reverse is true in hyperpotassemia. I don't know exactly what this means, but Solomon at Harvard has shown that if he blocks influx of potassium with ouabain in human erythrocytes he can show the same effect by varying the potassium in the medium. Thus this must be a true effect of potassium in the medium affecting digitalis action on potassium flux. On the basis of the hypothesis expressed this morning, if we lower the potassium, quinidine becomes less effective. This is just the opposite. I know of no cases in the literature where anyone has taken this into consideration in therapy with quinidine. I was talking to Dr. Elliott Newman at Vanderbilt. He said that they had one patient in whom hypopotassemia developed in the presence of quinidine. Under these conditions an arrhythmia reappeared. This may be very important. From a practical point of view if you had a patient resistant to quinidine, the obvious thing would be to give him some potassium chloride intravenously.

Question: What is the usefulness of the heart-lung preparation in pharmacology laboratory instruction?

Dr. Rushmer: I think it depends on what you're after. My point of view is that studies on the heart-lung preparations give some idea of what the potentialities of the heart might be when the heart is controlled by the investigator. In other words, the investigator himself is inducing the change which requires that the heart do something different. In this sense then, the heart in this circumstance can be studied so far as its potentialities are concerned, but not so far as its normal function is concerned. So, fundamentally, if one desires studies which indicate what the heart can do in response to a drug, this is a perfectly adequate preparation. But I think it might be an excessive step to try to judge from the response of the heart in the Starling heart-lung preparation what the intact individual will do. In instances we've seen, one cannot accurately predict what would be the cardiac response in the intact individual on the basis of information gained from the heart-lung preparation.

Dr. Keasling: Your techniques are beautiful and show responses to drugs very nicely. But I have neither the knowledge nor the facilities for such instrumentation and yet I must teach a laboratory course. If the heart-lung preparation will not give us the information we're after, would we be better off to attempt to use more refined apparatus such as you describe?

Dr. Rushmer: Dr. West has used some modifications of our general approach in some of his teaching. I will say that I have never advocated our procedures for teaching purposes. Yet I do use motion pictures of what we do for teaching in physiology. For example, the effect of epinephrine on the heart is to cause acceleration. This is the direct effect on the heart itself, but the effect is not acceleration in the intact dog and it may or may not be in the human. The thing I'm getting at is that you come up with two different answers fundamentally, and if your demonstration is one which misleads the student so that his conclusion is wrong, then I think that is bad teaching. I think our responsibility lies in simplifying the techniques we use in those instances where they could be valuable teaching devices useful in student laboratories. I don't think this is out of the question at all.

Question: But could you not get this same sort of information if you simply took an ECG on an intact dog?

Dr. Rushmer: Let me give you another example. If you read the standard textbooks about the response of the heart to an increased load, you come to the conclusion that the heart becomes larger. Our conclusion is exactly the reverse. Our experiments indicate that the size of the left ventricle is maximum when the dog is lying at rest in the horizontal position. Anything you do beyond this causes the heart to become smaller, not larger. I say that if as a result of an ordinary experiment such as the heart-lung preparation, you come to the conclusion that the heart always will become larger with an increased load, then the experiment is wrong.

Dr. Holland: I would say that the heart is in a failing condition in the heart-lung preparation. Would you say that the dog was in congestive failure?

Dr. Rushmer: May I just state this: that the heart is maximum size in the resting condition has been confirmed by radiographic techniques repeatedly in humans. In other words, in normal humans this is also true; so, fundamentally, a lot of our teaching has been wrong, partly because our research techniques have been giving us the wrong answers.

Dr. West: We did not intend, necessarily, that all the techniques mentioned here could be taken back into the laboratories of pharmacy schools. We did hope to introduce some new material that may not be generally known. The points we've been talking about cannot be looked on as background information to help clarify the things you can do. For example, I would not expect you to rush back and start fashioning microelectrodes for purposes of student demonstrations. However, an experiment that can be done simply with the aid of one stimulator and a simple electrocardiograph is the procedure described by Dr. Holland for the demonstration of arrhythmias in isolated atria. With the background information obtained from more refined experimental apparatus, the initiation and control of the arrhythmias may be explained to the students so that they may more intelligently view the results of the simple experiment. I think this is the same sort of thing that Dr. Rushmer does when he uses films as examples of his experimental work. Of course he has not put his medical students through the elaborate procedure of placing crystals on dogs' hearts in the student laboratory exercises.

Dr. Kroeger: (Described the use of rather elaborate electronic recording devices in routine student laboratory experiments.)

Dr. West: Although newer equipment is available in some areas it doesn't mean the kymograph must be outmoded. The best apparatus, from the students' standpoint may be the simplest apparatus.

Dr. Adams: I have seen students spend four hours setting up apparatus and five minutes studying the principle motivating the experiment.

Dr. West: I'm not really sure in my own mind what the objectives of the laboratory course are. If you are right that the appreciation of purpose, rather than methodology, of experimentation is the main reason for a student laboratory, then very simple laboratory procedures might suffice.

Dr. Holland: I feel that the laboratory, as Dr. Adams says, can be made simple enough where these principles can define for the student. I think in the graduate training of pharmacy and medical students, the laboratory should be prepared ahead of time. Then the student can have time to think more about the principle he's demonstrating and less time to engage in the methodology of the laboratory.

Dr. Rushmer: Different people use laboratories for different purposes. My personal approach to a lab is to give the student the opportunity to find out where physiologic information comes from--not where it came from fifty years ago, but now. Fundamentally, it seems to me that one doesn't learn general principles in the lab as well as he learns the sources of variability . . . Why doesn't he always get the same answer? What are the problems of instrumentation? How can one person get one answer and someone else get an exactly opposite answer? It seems to me that from this point of view you'd learn more in a laboratory using equipment similar to modern research apparatus than you would from using the outmoded stuff of fifty years ago. From this point of view, if you want to use this as your objective, you'd set up an entirely different kind of lab.

Dr. Holland: I would like to take issue. I agree that an electronic gadget that costs $6,000 is an ideal instrument for mass education, but certainly not for scholarly pursuits. This is a real problem in this country--how fast can we educate people and how efficiently can we do it? But I must remind you that the mind that designed the pyramid designed the atomic bomb. You'd be surprised how closely Overton came, between 1900 and 1910, to preparing a complete hypothesis of what we know now about the autonomic nervous system. It took the design of the vacuum tube to prove it. What we are substituting today, I believe, is instruments for good old hard logic. I believe that logic is what you must instill in the student if you expect maximum performance in the future.

Dr. West: We shouldn't use a technique because it's traditional, necessarily, and there does seem to be some tendency to do that. I would much prefer to record blood pressure on some sort of recorder that actually shows systolic and diastolic pressure, rather than with the traditional mercury manometer. It makes for better teaching. A lot of this controversy hinges around the availability of funds for the equipment one would like to use. Dr. Kroeger is fortunate in having access to a variety of refined instruments for student lab use.

(During discussion, the Langendorf preparation was mentioned.)

Dr. Holland: With the Langendorf preparation you can very adequately demonstrate the effects of digitalis, how it produces an effect on contractile force and how the variation of the venous pressure and certain other things affect this response. Now a few years back, Professor McMichael in England, said that digitalis glycosides produced their effects on the heart by modifying venous pressure, probably through some reflex mechanism. Well, this was done in humans and was obviously wrong. This is an example of why certain things done in humans don't give you the right answer. You can demonstrate the effect of glycosides in the isolated cat's papillary muscle which has nothing to do with venous pressure. I believe that the pharmacologist has a job to teach the student the mode of

action of drugs in the best way he can, and that the best way to do that is through simple procedures. I think, too, that some people will argue the difference between applied and pure research (if it's a benefit to mankind it's applied, and if it's a search for truth, it's pure). But I do agree with Dr. Rushmer that if a drug is to be used in a human being, then that's the organism to use for determining the drug's action in the human. Obviously then you must have masterly techniques and ingenious methods to do this because you cannot take out a human heart and attach it to a canula. I believe there are rules against that. You must have some philosophy for teaching students. I believe pharmacology's main purpose is the study of the mode of action of drugs and the best way we can do that is to use animal experimentation with the simplest methods available.

Dr. Meyers: So often we are trying to demonstrate at the descriptive level the action of a drug. Now take digitalis as an example. No matter how complete our knowledge of contractile protein finally becomes it still will be essential to discuss the several ways by which digitalis can slow the pulse. If you're going to demonstrate drugs at the descriptive level you can use the human well. In the limited time we have, how much of this are we obligated to teach? Of course, we have to teach accurately. I think there's no excuse for anyone in here to say that Starling's Law is applicable in every situation.

Dr. Holland: I agree. But what I'm getting at is that as far as pharmacology is concerned we don't have to rely on the human as an experimental organism to study the mode of action of drugs. If these drugs are to be used in the human, then extrapolation from a dog experiment or from a Langendorf heart is certainly a fallacious event.

Question: Do you suggest, Dr. Holland, that cardiac glycosides should first be screened in man?

Dr. Holland: Well, if you're going to use cardiac glycosides in man it's all right with me. But if I want to know how digitalis acts I'm not forced to use a human because I may get the wrong idea of the truth. I think McMichael's observations are classical examples of this.

Dr. Rushmer: Take ten different people, present them with ten different items of data and you get ten different concepts potentially out of them. I think that one wants to realize that there is a human element in one's final interpretation of experimental data. I wouldn't go along with this idea of using humans to screen drugs until toxicity effects were known. But I would agree with you that the human application is the final test that you may have to do.

Dr. Haley: The current textbooks are going to give the student an awful lot of human pharmacology. In other words, the pharmacist is going to discuss the information that he derives from his textbook. That textbook is going to be slanted toward the use of drugs in the human being. Basically a student laboratory is there to point out to the student that certain of the principles that have been discussed in the lecture period can be demonstrated in animals. I see nothing wrong with this. Every drug house in the country standardizes drugs by what they will do in animals, whether it's a toxic principle, affects blood

coagulation, whether it causes hypotension or ganglionic blockade. All this is done prior to the time they go to the clinical staff with the drug to have someone make a trial run of the drug on a human being. Now, the first thing we deal with is the pure research that goes on in our laboratories. This is an entirely different subject than the one where we're dealing with the average student. In this case it may be a series of experiments that demonstrate certain particular things of which we have a fresh idea, and whether that particular idea is correct; or it may be for the purpose of training the graduate students. To get back to the screening of drugs on humans: In the field of cardiac glycosides, Dr. Harry Gold proposed that all cardiac glycosides that were for use in human beings be standardized on humans. If I recall correctly, at the present time they are standardized on pigeons.

Dr. West: Dr. Haley's point tends to reorganize or reform the areas in which we should be talking. I believe that Dr. Holland has tried to point this out, also, in terms of the pure research aspect of graduate student programs, as opposed to the teaching effort for medical or pharmacy students.

Dr. White: Dr. Holland, do you have any idea as to what happens on a cellular basis when a toxic dose of digitalis is injected?

Dr. Holland: No, I wish I did. But I believe that the best way to present the matter is at that particular level, or below that. You see, you can classify drug action at different levels: organismic, cellular, subcellular, etc. For example, you can say that the mode of action of penicillin is that the patient with pneumococcal pneumonia gets well.

Dr. White: But you have talked about this matter of permeability and I just wondered if that would be involved.

Dr. Holland: In toxic doses the permeability of the cell is modified. In therapeutic doses it's difficult to say. I don't think our techniques are sensitive enough to tell us. But I do feel that this is how the glycosides, in the final analysis, act. Observations of actomyosin threads show that contractile effects can be produced by substances such as cholesterol which certainly do not produce the characteristic effects of digitalis. Again, this may be a permeability phenomenon--perhaps cholesterol doesn't get into the muscle cell. This may be a true steroid effect.

Dr. West: I don't think that Dr. Holland would like for us to go away thinking that all digitalis effects have to be in terms of membrane permeability. There is good reason yet for thinking that contraction and membrane activity must be inseparably linked.

Question: (The possibility of prophylactic use of digitalis in elderly individuals was referred to the panel for comments.)

Dr. Holland: This is like the old man of ninety years who was told by his doctor to stop smoking. Later on the grandson was talking to the doctor who asked, "What happened to your granddad?" He was told, "The poor old soul died from smoking." You'd probably find out that you would have a lot of earlier funerals in a number of people if you gave them digitalis from a prophylactic point of view.

Hajdu at the National Institute of Health made an observation. He was able to isolate a lipic component from myocardial tissue and serum which could be added to the hypodynamic heart with beneficial results. They proved the structure of this compound. This is interesting because thirty years ago A. G. Clark made a similar observation. He perfused isolated frog heart and found that a lipid material was removed which he could concentrate. He suggested that this was a lecithin, which is just exactly what Hajdu's people are dealing with. So once again it's very good to read the literature.

Dr. West: I'd like to thank the members of the panel and the audience for the fine session we've had this afternoon. There will be demonstrations of these remotely applicable experimental procedures in the designated rooms.

Thank you very much for your attendance.

Thursday Session

CURRENT CONCEPTS IN PSYCHOPHARMACOLOGY

James M. Dille

Chairman

INTRODUCTION

James M. Dille

University of Washington

This morning I am before you in a double role. It is my duty to act as chairman for the session today and my privilege to present an introduction to the subject of today's program, and so with due modesty, I introduce the first speaker.

First, I would like to give some attention to the ways of thinking about mental illness. We think about any disease from two standpoints, (1) its basic nature and (2) its treatment. The second can only grow out of the sound knowledge of the first.

We are in now what might be called the fourth era of thought about mental disease. The first era began in ancient times and can be called the era of magic. Mental illness was attributed to evil spirits and the treatment was, logically, the use of magic in the forms of incantations, charms, casting of spells, and so forth. This concept prevailed until fairly recent times and, of course, no credence is placed in the ideas of this period now.

The second era began in the early part of the nineteenth century. Medical scientists at this time were concerned principally with the ways in which disease processes modified the growth of microscopic structures of the body. This was the era of the great Viennese pathologist. At this time Rokitansky and his colleagues performed post mortem examinations on several thousand patients a year. No one can minimize the importance of this approach to an understanding of disease because this explained how disease modified the structure and, consequently, the function of the body. During this era there was a search for some morphological change which could be associated with insanity. This search proved completely fruitless. It was impossible to find any changes in the structures of the brain which could be related to, for example, the striking symptoms of a manic psychosis. So, successful as this period might have been in relating such things as tuberculosis or pneumonia to pathological changes, it failed to help in understanding the cause of insanity. As the years went by this approach was so unrewarding that the time was ripe for a new concept.

The third era began at the turn of the century and came about through the writings and the work of Sigmund Freud. We are seeing the effects of his concepts. It is difficult to summarize the contributions of Sigmund Freud regarding the conception of the nature of mental illness or to follow the modifications of his concepts by his contemporaries and his students. Essentially, he removed mental illness from the physical to the psychic. Some say to the undefinable mystical. However this may be, he furnished a system of rational explanation out of which came the psychoanalytical method of therapy.

The fourth era has just begun. At a meeting a year ago in May of the American Psychiatric Association where Doctors Heath, Pauling and Bailey cast doubts on the concepts and methods of psychoanalysis and advanced the idea that mental illness is the result of disturbed body chemistry. The controversy is going on and we will watch with a great deal of interest what develops from it. It is interesting to observe that whereas the pathologists of the early nineteenth century failed to find a structural abnormality in insanity, we are now looking for a biochemical abnormality in mental illness.

Next, let us consider the nature of mental disease. Let us think of an animal species, homc sapiens, living on the face of the planet Earth. We find that this species operates in a certain behavioral way to bring about a state of general efficiency of the species. However, if we observe closely we find that certain individuals behave differently from the majority. The individual who does not behave in an acceptable fashion with respect to the behavior of the majority of the group presents us with our first job. This is a description of aberrant behavior. This is the problem of characterizing the abnormal behavior which we call insanity, mental illness or mental disease. We find that we can classify this into three groups. The first of these is psychoneuroses; the second, character disorder, and the third, psychoses.

With acknowledgment to Dr. Tom Holmes of our Department of Psychiatry, who is an original thinker in this field, I would like to consider these three classes of mental illness. First, how does a normal individual behave? We can say that the normal individual does the right thing at the right time and for the right reason. The psychoneurotic departs from these three criteria in the following way. He may do the right thing at the right time, but for the wrong reason. This makes psychoneuroses extremely difficult to diagnose and to characterize because the reason is something intimate, personal, and deep within the individual. Perhaps this can best be shown by example: Let us consider homicide. At first you would say that murder is wrong. However, under certain conditions it is normal to carry out homicide. This is in time of war. In wartime the act of killing is appropriate if one kills an enemy. The time is appropriate if it takes place during battle. And the reason is patriotism. A psychoneurotic might outwardly meet all of these requirements except the last one. He might kill because of a sadistic satisfaction in himself instead of because of patriotism. This means that he would be motivated by the wrong reason.

You will notice that I have used the words "appropriate" or "inappropriate" rather than the words "right" or "wrong." The terms "right" and "wrong" carry implications about what is good or what is evil. This brings the aspect of religion into the picture because in many religions, what is regarded as wrong may simply be inappropriate in the interpretation of the dogma of the religious sect. For example, certain religious groups forbid the use of alcoholic beverages, coffee, cigarettes. Yet these things are quite all right in other religious groups. So what is wrong or sinful in certain social settings and therefore termed inappropriate behavior, might be appropriate in another social setting.

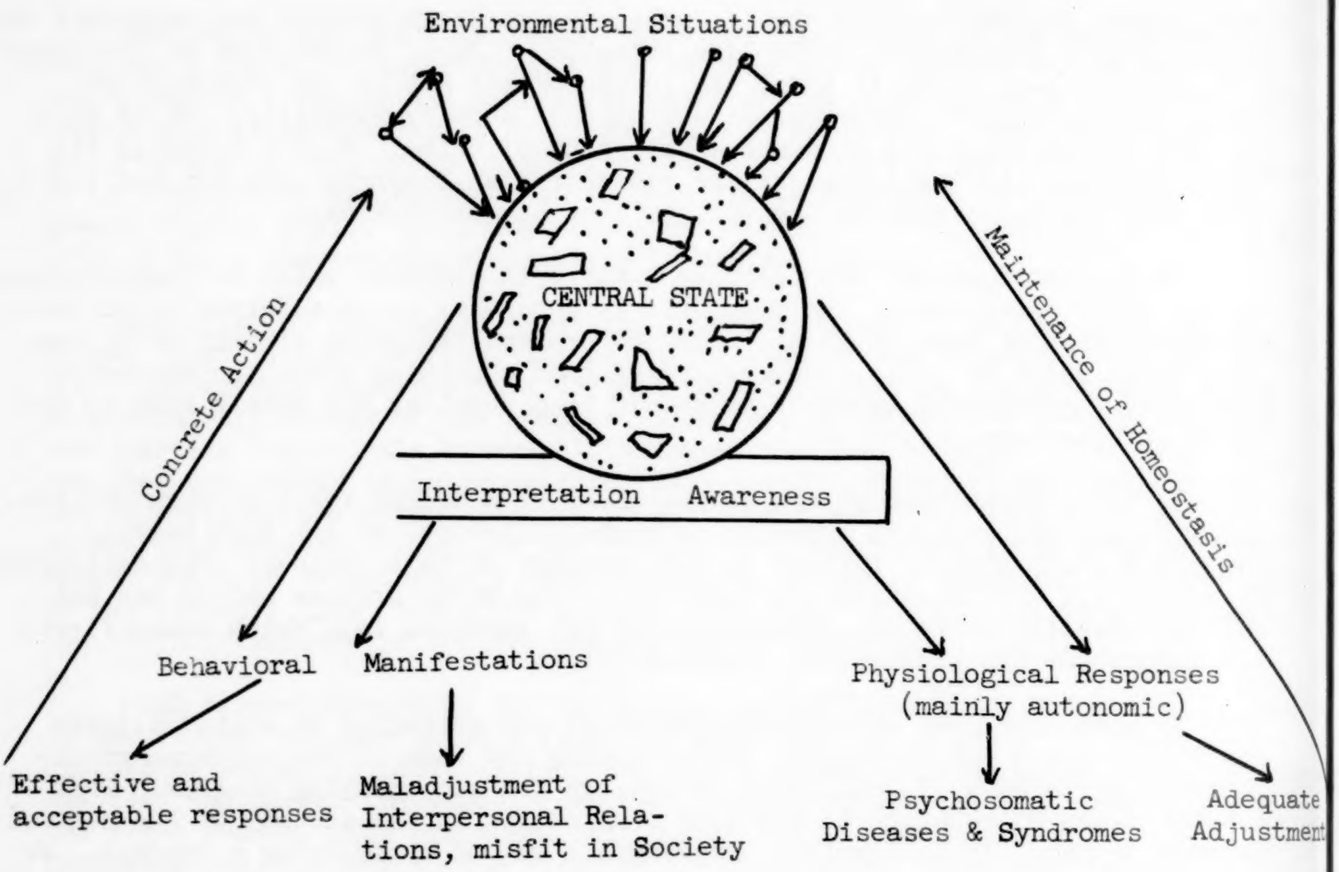
In the category of the character disorder there is inability to recognize the appropriate act and the appropriate time. Such individuals may appear

intelligent and emotionally stable and appear to their friends and neighbors to be quite well adjusted to their life situation. Here, in addition to the inappropriate reason, there is added the inappropriate act or the inappropriate time. The newspapers report senseless murders done by juveniles. It is hard for the normal person to understand this kind of crime. Such a mentally ill individual has had the inappropriate reason for an inappropriate act and since such acts are violations to the society they become criminal.

In the third group, the psychoses, there is behavior which is inappropriate in all three categories. The psychotic is generally so maladjusted to his environment that he must be incarcerated to prevent damage to himself or to the society in which he lives. Understanding then something about the characteristics of the abnormal behavior we should then consider why people come to develop this abnormality.

At the present time we are in the midst of a search for a biochemical ideology to explain abnormal behavior or mental illness. We are also hearing something about genetic factors in the ideology of this illness. Unquestionably this has made a stimulating new approach to the whole problem but it has not been universally accepted. Fundamentally the question is, "Which comes first, the illness or the biochemical abnormality?"

To summarize some of the thinking about the mechanism of mental illness and to develop a possibility of understanding how some of the psychopharmacological agents work, I would like to present the accompanying diagram. This diagram bears no relation to anything that exists in the anatomy of the central nervous system. It is simply a diagrammatic way of symbolizing a concept. We should accept this without too much difficulty because as scientists we are continually dealing with this kind of symbolism. I need only to call to your attention the symbol for the benzene ring. The straight lines and small curves which we put down on paper are obviously not the benzene ring as it is found in nature. Yet by common consent we have all accepted this pencil and paper symbol for the real molecular configuration of benzene. This accompanying diagram represents a central state of an individual seen within the large circle. It can be thought of as being in equilibrium when conditions are normal. This equilibrium is not a static thing but rather a continual fluxing state. Impinging on this central balanced state of the individual are all sorts of environmental situations represented by the moving dots above the large circle. These environmental situations affect the central state of the individual for better or for worse. We sometimes think of these environmental situations as being good or being bad and we speak of "good luck" happening to us or "bad luck" happening to us. But these environmental situations are completely indifferent to the individuals. They just happen. They are neither good nor evil and their impingement on the individual is coincidental. The individual has the ability to incorporate into the fluxing central state these environmental changes and to store them in the form of memories. Out of this central state then comes awareness and interpretation by memories of the environmental changes. This means that the individual may consciously or unconsciously analyze and react to the environmental situations. The outflow from the central state takes two pathways. The first, shown on the right, is physiological and serves to maintain homeostasis in the individual. If the physiological responses are



inadequate, psychosomatic diseases and syndromes may develop. Reactions of the individual to the environment by behavioral manifestations are shown on the left. The individual may do something which leads to concrete action and the resulting modification of the environment. If these behavioral adjustments are appropriate and adequate the individual makes an adjustment to his environment. If they are inadequate or inappropriate he may become a misfit in the society and attention will be called to this behavior.

The psychopharmacological agents can be thought of as affecting the fluxing turmoil which is going on in the central state. Probably the psychotomometic drugs operate in some way to facilitate the connections of the units of the central state. This facilitation may be a useful thing to a point, but too great an effect could result in hallucinations and disruption of logical thinking. On the other hand, the tranquilizing drugs can be thought of as slowing turmoil of the central state and settling it down the pathways from an abnormally high state of function to normal.

With this kind of concept the problem facing the pharmacologist working in this area is the development of new techniques and methods for the evaluation of first, the psychological functioning of the central state of the individual, and second, the use of these measurements to determine how these new psychopharmacological agents bring about modifications of this state.

MOOD-ALTERING DRUGS

Chauncey D. Leake

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While the practical success has been fairly great with the new mood-altering drugs, which were introduced so dramatically only a few years ago, more important in the long run, perhaps, will be their stimulus to basic research on the way our complicated higher nervous systems work. These drugs have helped to focus attention on the vast amount of physiological and biochemical detail which has been slowly accumulating on central nervous system action. To get some idea of how these remarkable drugs may operate, it may be wise to remind ourselves of some of the physiological and biochemical factors involved.

Physiological and Biochemical Factors

Outstanding is the correlated anatomical and physiological data on the integration of central nervous system action through the extensive ramifications and cross-connections of the reticular system in the midbrain, as indicated so well by H. W. Magoun. This system is concerned with feeling, and the reflex or automatic responses to sensory stimulus. It is greatly implicated in conditioning, and importantly in the basic emotions. Whatever physico-chemical processes are set up in the reticular system by incoming stimuli, they are quickly relayed to the sensory cortex for such perception as may be given them, and they are also spread around the brain stem, for correlation of muscle or gland action in reflex response, and further, they act on the pituitary complex.

Adaptive responses of mammals to stimuli removed from their bodies, as in sight, sound or smell, or to sensations referred to their bodies from skin, mucous membranes or viscera, and especially from muscles and joints, are seemingly developed from experience by conditioning, or learning, and seem to become patterned. For stimuli that are associated with possible harm come the feelings of anxiety or fear, with responses mediated chemically, as well as nervously, as shown by Cannon, and by Selye. If the situation appears acute, the response may be the "flight or fight" reaction, described by Cannon, wherein release of epinephrine and norepinephrine from adrenergic depots, gives peripheral responses of increased muscle tone and contractility, blood coagulability, blood sugar, respiration, heart action, and blood pressure, but with relaxation of bowel and bronchi. These responses are over-all protective for emergencies. On the other hand, if the situation is prolonged, as in cold, or continued stress, the anterior pituitary releases a number of trophic chemicals which may give more prolonged adaptation, as Selye indicates. The adrenocorticotrophic hormone, ACTH, stimulates the adrenal cortex to release the corticosteroids, which maintain water and electrolyte balance in cells, helping to minimize local injury and promoting healing. The thyrotropic hormone gets the thyroid to secrete more vigorously, promoting cellular metabolism, and increasing muscle and nerve activity. And there are further effects on sugar metabolism, and sex function.

In all this complex of activity, there is evidence of an elaborate feed-back mechanism, which partially regulates the extent of peripheral muscle and glandular activity. This comes in large part from the proprioceptive sensory stimuli from muscles and joints, and some of it spills over to the cortex, increasing alertness and awareness, promoting wakefulness and attention.

It is amazing how little of the sensory stimulation which bombards the mid-brain seeps through to consciousness. The function of the cortex is frequently confusing, and in spite of the seeming clarity with which we can understand its operation, it continues to elude our ability to analyze it satisfactorily. Primarily, as Sechenov showed long ago, the stimulation of the cortex tends to inhibit the lower reflex activity of the lower parts of the central nervous system. Physiological measurements suggest that there is greater physiological activity of the cortex in sleep than in wakefulness. It is to be remembered that we still know very little about sleep, although we spend a third of our lives in that state. However, the cortex also is an amazing area for sorting out incoming stimuli, classifying them automatically, and relating them in patterns which seem to correspond to the physical world around us.

The isolation of the brain from the rest of the body is now realized chemically in connection with what is called the blood-brain barrier. No anatomical structure this, but rather a graded system of enzyme concentration which allows only some kinds of chemicals to get in contact with brain cells, unless the chemicals come in overwhelming concentration. Thus, although the peripheral action of epinephrine on muscle tone increases alertness and attentiveness, by proprioceptive nervous bombardment, the direct application of even very small amounts to the brain, through the lateral ventricles, results, as shown by Feldberg and Sherwood, in muscle relaxation, incoordination, semi-sleep, and withdrawal. When oppossums and armadillos curl up and lie still in the face of acute danger, they may be showing the result of genetic lack of blood-brain barrier, or of an overwhelming flood of epinephrine to their brains. However, let's remember that some tough soldiers also go limp in the face of acute danger.

Some of the significant physiological factors in central nervous system functioning, which are capable of being modified by drugs thus seem to be (1) the integrative ramifications of the reticular system in the brain stem; (2) a complex of peripheral feed-back mechanisms, especially of proprioceptive impulses from muscles and joints; (3) the analytical, inhibitory and regulatory action of the cortex; (4) a complex of reflex conditioning; (5) nervous action on the pituitary-adrenal axis, with hormonal effects through epinephrine, corticosteroids, and thyroid secretion, and (6) the stability of the blood-brain barrier. Derangements of these factors may result from metabolic disturbances, or from drugs which may alter usual metabolic pathways. The results may be overall depression and sluggishness, anesthesia or schizophrenia, or, on the other hand, increased irritability, excitement, and convulsive tendencies. Drugs exist which may cause either extreme.

Some of the biochemical details of the situation are beginning to become apparent, even at cellular levels. We are learning about neurohumoral transmission, with cholinergic neurons rich in acetylcholine and choline esterases, and with adrenergic neurons rich in epinephrine and norepinephrine, with the amine oxidases and phenol oxidases which control their concentrations.

The more we learn about the complex biochemistry and physiology of the nerve cells and their processes which make such a confusing jumble in our brains, the better will we be able to describe how it is that so many different types of chemicals can so significantly alter mood and behavior. Drugs which affect mood and brain function may act directly by combining with molecules in the cells in the brain; but they may also act in part by influencing muscle-tone, with resulting changes in nervous feed-back to the brain stem reticular alerting system, or they may act on endocrine glands, and thus influence brain action indirectly, or they may act through altering blood flow in the brain, or enzyme action in the brain cells, or by increasing or decreasing the rate of transmission of nervous impulses across synapses, as shown by Marrazzi and Hart. More and more will it be wise to try to focus attention on the molecular reactions of drugs with molecules in cells, for it is only at a molecular level that chemical reactions can be understood. This factor is sharpening interest on the molecular structure of cells, and important ideas in this regard may soon be emerging, as staining effects, specific analyses, and enzymic reactions are correlated with structural components as chromosomes, mitochondria, granules, and phase-boundaries.

Interest is arising in the ratio of intracellular to extracellular electrolytes and metabolites in relation to brain function. The importance of sodium ion migration in relation to nerve conduction is well appreciated. This serves to control, in part, the change on the surface of the nerve trunk, which alters diphasically in nerve transmission. It seems that calcium is also important in the balanced functioning of the nerve cell membranes. It seems that metabolic increases within the nerve and muscle cells of such substances as 5-hydroxytryptamine, adenosine-triphosphate, and histamine, may be associated with increased tension and capacity for discharge. When the threshold for discharge is reached, these kinds of compounds may escape from the cell, increasing extracellular concentration of depolarizing agents, with resulting refractoriness for a short period, until the metabolic process repeats. The leakage of such metabolites from the nerve cells may maintain the balance between capacity for firing and refractoriness or inability to fire at all. Increased intracellular concentration of such compounds may be associated with increased tension, nerve transmission, and alertness or speeded-up nervous response. Increased extracellular concentration of these kinds of compounds may result in lowered tension, more sluggish responses, and relaxation. It is interesting that Brodie and his associates have shown that reserpine releases 5-hydroxytryptamine and norepinephrine from the cells of the brain stem, while it is well known that the anti-histaminic drugs are generally depressant in action.

States of Central Nervous System Activity

The general scope of central nervous system activity has been well studied for over a century, since Snow first defined "states of narcotism." The average range of central nervous system activity is correlated with average pulse, respiration, blood pressure, pupil size, reflex or conditioned reaction time, and muscle tone. These physiological variables can be readily measured, with the exception of muscle tone. Some method of measuring muscle tone would help greatly in estimating the over-all condition of central nervous system functioning, since increased muscle tone or tension seems to go along with jitteriness,

anxiety, emotional reaction, and a tendency toward a manic or even convulsive state. On the other hand, muscle relaxation seems to go along with emotional ease, apathy, indifference, and intellectual sluggishness.

Similarly cardio-vascular and respiratory function seems to correlate with general central nervous system functioning, indicating considerable viscera-cortical relationship, a matter under intensive study by the Russian physiologists. Increased pulse, blood pressure, respiration, and speeded-up reaction time, along with increased muscle tone, are symptoms of the excited state, and tend to move toward anxiety, tension, jitteriness, and the manic or convulsive condition. Many drugs produce these same viscero-cortical signs: the alkylamines or sympathomimetic drugs like epinephrine, amphetamine, ephedrine; cocaine and the local anesthetics generally, which tend to activate the sympathetic nervous system; strychnine, which facilitates synaptic transmission between nerves; metrazol, nikethamide, picrotoxin, which stimulate the brain stem and medullary reticular alerting systems, and the caffeines which facilitate cortical transmission, and activate the alerting system of the mid-brain. More recently, milder and slower-acting central stimulants have been developed in pipradrol ("Meretran"), and in methyl-phenidyl acetate ("Ritalin"). The milder and slower action of the latter make them useful as mood altering drugs, promoting increased alertness in depressed conditions. The amphetamines are also very helpful in chronic depressed states, and indeed are almost specific for such obscure diseases as narcolepsy. The amphetamines increase muscle tone, and may act in part by increasing the feed-back from joints and muscles, thus stimulating the reticular alerting system of the brain stem. There is evidence also that they may directly stimulate such specific centers in the mid-brain as the inhibitory center for food intake, as shown by Broback.

On the other hand, in considering levels of depression, one may follow the anesthetists in defining several levels progressing toward anesthesia and coma. The first, going down from the average "normal" state of wakefulness, is <u>relaxation</u>, in which muscle tone is less than usual, and in which there is a tendency for pulse, blood pressure, and respiration to diminish, along with the speed of reflex reaction. If the diminution in these functions is still more marked, the condition may be called <u>depression</u>, where the individual is apathetic, with sluggish responses, and considerable muscle relaxation. If the situation goes progressively downward, the reactions tend to become incoordinated, with varying muscle tone, pulse, blood pressure, and respiration. This is the state of <u>delirium</u>, where there is only semi-consciousness, and where response is quite uncoordinated. The next level downward is <u>anesthesia</u>, where there is no response, no reflex reaction, complete loss of muscle tone and consciousness, with no sensation, but with average pulse, blood pressure, and respiration. When these visceral functions diminish the tendency is toward <u>coma</u>.

This progressive downward trend of physiological function can be brought about by many drugs, some acting swiftly, as the inhalation anesthetics, ether, chloroform, nitrous oxide, divinyl ether, and cyclopropane, while others act more slowly, as the alcohols, the chlorals, the barbitals, the bromides. In each instance, however, the effect on the individual is directly proportional to the dose, with modification by the rate of absorption in relation to the rate of metabolic destruction in or removal from the body.

While there are many modifications of the chief simple depressant or sleep-producing drugs, they generally have one basic action in common in relaxing muscles, and in slowing reaction time. This action occurs incidentally in drugs whose chief use is in relieving pain, like the analgesics. These were first developed as substitutes for quinine when its high price, resulting from the destruction of the Peruvian cinchona forests, gave the incentive to get something to take its place. The salicylates were found to have antipyretic action, and the acetanilids and amidopyrines followed. Their action in relieving congestive pain was analyzed by Barbour in showing their ability to release water from cells swollen by allergy. The relaxing and mildly depressing action of the salicylates is usually sought in cases of tension headaches and the like.

The marked pain-relieving properties of the morphine compounds is also associated with progressive depression with increased dosage. These drugs may often show a slight initial nauseating effect, with transient confusion, with subsequent relaxation and euphoria. In these drugs the action is directly on the brain stem and cortex, in blunting the sensation of pain.

We have then a large variety of chemicals which progressively depress the central nervous system in relation to dose. They seem to produce the same general effects through many different ways of action. More recently, the antihistaminic drugs, developed by Fourneau and Bovet, have been recognized to have significant relaxing and depressant effects. These drugs may have actions in addition to blocking histamine: chlorpromazine, according to Grenell, releases adenosine triphosphate from the cells of the brain stem.

While the states of activity of the central nervous system may roughly be judged by the symptoms exhibited by the patient, more objective information can be obtained by electroencephalographic studies. These are useful in psychiatric conditions, and indeed now are being utilized with sufficient skill in connection with anesthesia to provide servo-control mechanisms for managing the administration of anesthetic vapors. However, it is not yet possible to obtain action currents from the particulate portions of the brain and brain stem in the intact mammal or man. The extensive studies now being made on experimental animals and even on humans on these matters is helping to localize specific centers for the nervous control of specific functions and even for the emotional reactions associated with them. These investigations are helping to localize the specific actions of various kinds of central-nervous-system-acting drugs, whether stimulating or depressing.

Hallucinating Drugs

The various new depressant or tranquilizing drugs have had startling effectiveness in relation to mental disorder. Attention was directed toward this usefulness by the dramatic reports on lysergic acid diethylamide from Stoll and his associates in Basle. This compound was accidentally found to have marked effects in reproducing the symptoms of schizophrenia in amazingly small dosage. This fact at once led to a renewed interest in the many anciently known hallucinogenic drugs, with a marked change in attitude toward experimentation with them.

One of the best reviews of hallucinogenic drugs is that prepared by the great toxicologist Louis Lewin (1850-1929), which was published in English under the title, "Phantastica: Narcotic and Stimulating Drugs; Their Use and Abuse." This surveyed the long social history of indigenous drugs used by different peoples over the world for exultation, or for psychological effects in religious rites. It included accounts of fermented beverages as beers and wines, which were known from antiquity, and distilled liquors as introduced by the medieval Arabs, together with cannabis, opium, coca, coffee, tobacco, peyote, ordeal poisons, and various hypnotic and anesthetic agents. Lewin clearly emphasized the social regulations imposed by tabu or religious ritual in the use of such agents by primitive peoples. Francisco Guerra has recently prepared a similar volume covering the hallucinogenic drugs of Mexico, and Howard Fabing has also written on the matter.

In the effort to learn about the causes and characteristics of mental disorders it has suddenly become fashionable to study drug induced aberrations of mental behavior. This is a difficult field for scientific investigation, since so many uncontrollable variables are present. Some of these have been studies by Beecher and Lasagna and their associates. They find a surprising amount of subjective response to placebos on the part of susceptible subjects, with many reactions seemingly dependent on the relation between the patient and the physician who may be concerned. If patients have marked confidence in their physicians, for instance, it can readily be shown by double-blind experimental methods that patients will get marked pain relief if they expect to do so from simple lactose placebos.

Nevertheless, work with well-known hallucinogenic drugs as mescaline, lysergic acid diethylamide, bufotenine, and adrenolutin, has resulted in clues indicating some of the complexities of metabolic, endocrine, and nervous factors that are involved in mental disorder. Some think that metabolic malfunction predominates, with disturbances in epinephrine metabolism to produce hallucinogenic compounds like adrenolutin. But the ideas of Hoffer, Osmond, and Smythies on this matter are readily verifiable. Woolley and Shaw focus on the indole nucleus of many hallucinogens as the significant factor, and think that serotonin metabolism is at fault. Some postulate a hypothetical substance, "taraxein," as being responsible, but confirmation is not readily obtained. Many find disturbances in ascorbic acid metabolism, as reflected in the ceruloplasmin level, in mental disease.

It is interesting that many of the characteristic effects of the hallucinogenic drugs can be noted as transitory phases in the action of many depressant agents, such as the morphine compounds, the alcohols, and the barbitals. These effects are chiefly the un-coordinated nervous responses observed in the delirium stage of depressant action of the general anesthetics. It is in this stage that disturbances of sensation, involving hallucinations, appear.

The New Tranquilizing Agents

There are several types of new drugs that may be called "tranquilizers." Some are new barbital derivatives; others are carbamides; some are chiefly

The Chief Tranquilizing Drugs

The major tranquilizing drugs are rapidly increasing in number and use. Berger classifies them as (1) autonomic depressants and (2) central nervous system relaxants. The autonomic depressants seem to be more useful in severe mental illness, including the psychoses, while the central nervous system relaxants with milder action may be preferable in the milder mental disorders.

The autonomic depressant agents include Rauwolfia alkaloids, phenathiazine derivatives, and diphenyl methane compounds. These agents alter the threshold to electro and chemical convulsions, potentiate hypnotic agents, block conditioned responses and cause atropine-like changes in EEG. The chief rauwolfia alkaloids now in use are reserpine and deserpine. The depressant phenathiazine compounds, which are antihistaminic, are chlorpromazine, promazine, mepazine, perphenazine, and prochlorperazine. The diphenyl methane depressants include benactyzine and hydroxyzine.

The central nervous system relaxants diminish manic or exaggerated responses, raise the threshold for electrical and chemical convulsions, but do not change conditioned reflexes or alter usual responses to stimuli. They include such drugs as meprobamate, phenaglycodol, ectylurea, and azocyclonol.

These agents have been fully discussed from the standpoint of their pharmacological actions and clinical uses in various symposia held under the auspices of the New York Academy of Medicine, and of the American Association for the Advancement of Science, as well as in such reviews as those offered by Fazekas, Toupin, and Alman. There are many excellent monographs on some of these compounds also.

Rauwolfia. Preparations of serpent root were used from antiquity in India for diarrhea and to quiet frenzy. It was described by Dioscorides, the surgeon in Nero's armies. But it was not until preliminary reports by Indian clinicians during the thirties appeared that much interest arose in the drug. Its chief alkaloids were described in 1952, and Bein reported on their hypotensive and sedative actions. At the New York Academy of Sciences Symposium in 1954 many clinical reports agreed on the value of reserpine as a hypotensive tranquilizing agent. Reserpine is a white crystalline compound containing many methoxy groups and an indole nucleus. Its solutions are photosensitive. It is readily absorbed from the alimentary tract, but its fate in the body is not known. It disappears from tissues in about six hours. Without local action, its effects appear slowly but are lasting. Brodie shows that it releases serotonin from cells, and its effects may be apparent until intracellular build-up of serotonin again occurs. Even in doses of 0.1 to 1 mg. it is markedly active. Blood pressure falls and tranquility occurs without sleepiness. It is well tolerated, but there may be nasal congestion, and in some instances depression may occur. Further there may be sodium and fluid retention, with tendency toward congestive failure. These untoward effects clear quickly on stopping administration. Reserpine is more helpful in acute schizophrenics than in chronic mental disorder. It controls tension, anxiety and fear, and its clinical use has been broad and valuable.

anticonvulsants, but the main interest is in those which are sometimes called "ataraxics," that is agents which will counteract excitement and mania, and which will produce a more tranquil relaxed quiet state. Further, it is to be remembered that the antihistaminics are well recognized as moderate tranquilizing agents, some of them being used as adjuncts to anesthesia with hypothermia, and all of them bringing caution about the possibility of relaxation, slowed reaction time, and lack of muscular coordination, if pushed too vigorously.

Most of these new drugs have been well characterized pharmacologically, and widely reported upon clinically. The pharmaceutical manufacturers who are interested in developing them have made available many expensively prepared and well-illustrated brochures to describe them. It is interesting, however, that the professional advertisements about them, as well as the brochures themselves minimize the essential scientific data that is so important in judging their relative value.

In addition to the details about the physico-chemical properties of new drugs, including structural formulae and chemical relationships, the essential scientific data comprises information on rates of absorption by different routes of administration, material on the fate of the drug in contact with living material, and precise figures on rates of destruction or removal from the body. These data are necessary in order to judge the requirement for repeated administration. Absolutely essential are quantitative data on toxicity, both by single administration and on repetition of dosage. Toxicity data should indicate the symptoms on single overdosage, or on accumulated dose, so that toxicity can readily be recognized. There should also be information on treating acute poisoning, or of symptoms from excessive repeated dosage. The toxicity data should be sufficient to yield reliable dose-effect curves, especially in relation to doses necessary for the desired effect. The ratio of ED_{99} to LD_1 should be used for estimating the safety margin, rather than the unreliable ratio of ED_{50} to LD_{50}. As much information as possible should be given regarding the site of action, and the mechanism of action at a cellular level as well as at an organ or system level. The action should be analyzed with regard to local effects at the point of administration, and then detailed regarding the responses of various organs and organ systems to the drug. Clinical indications for use should be based on the clearly demonstrated actions, as shown by experimental studies on a variety of species. Clinical results should be statistically analyzed to make sure that such variations as are described are really significant. Dosage forms and recommended preparations for clinical use should be fully explained, with reasons given for the choices made. With such information, the physician may be in a reasonable position to exercise the good clinical judgment expected of him in applying knowledge about a particular drug to its rational use in a particular individual patient.

Physicians should insist that pharmaceutical manufacturers supply them with this essential data on new drugs. Only in a few instances in regard to the new tranquilizers has this sort of knowledge emerged. When it is collected together in brochure form, it is usually arranged to give the best possible picture for the particular drug concerned, as is natural enough, but this is frequently done by suppressing useful comparative data, or by minimizing toxic dangers, or by neglecting to give satisfactory figures for dose-effect and time-concentration relations.

A related alkaloid is deserpidine, and it has similar actions. Ferguson finds that it is more helpful in chronic mental illness than is reserpine. Further it has fewer side effects. Deserpidine is given in doses of 0.1 mg. daily in mild anxiety, and in amounts of 2 to 3 mg. daily to hospitalized psychiatric patients.

Phenathiazine Tranquilizers. The development of antihistaminics by Fourneau and Bovet resulted in attention to phenathiazine derivatives which were found to have anti-Parkinsonism action and to cause central depression. Chlorpromazine was noteworthy in this regard, and after development by Rhone-Poulenc in France, was well promoted by Smith, Kline & French Laboratories in this country under the trade name "Thorazine." Chlorpromazine is a white crystalline substance, soluble as the hydrochloride, and rapidly absorbed and distributed in the body. It is metabolized in the liver and rapdily leaves the blood. Some is excreted as a sulfoxide in the urine. It has a mild local anesthetic action on mucous membranes, and its chief effect is a general sedation, with adrenergic blocking, and hypotension. The drug depresses the sensory areas of the reticular system, and causes an EEG pattern similar to that noted in sleep. It is antiemetic. Grenell noted that it releases adenosine triphosphate from the brain stem. Chlorpromazine is used in many clinical conditions as a sedative, as in nausea, alcoholism, and as an adjunct to anesthesia. Its chief use, however, is in psychiatric states. It is especially helpful in schizophrenia, but of little value in anxiety or depressed states. It reduces combativeness and frenzy. Recently it has been found almost specific in porphyria. Untoward reactions include hepatitis, dermatitis, and agranulocytosis. These are manifestations of allergy to the drug. The dose varies from 25 to 200 mg. daily, orally, or intramuscularly for rapid action.

Promazine (trade name "Sparine") is chlorpromazine without chlorine. Its pharmacology and clinical use are similar to those of chlorpromazine. It may have more allergic tendencies than chlorpromazine. Its dosage is 200 mg. by mouth or intramuscularly.

Mepazine (trade name "Pacatal") is a piperidyl derivative of phenathiazine, and has been widely used abroad. It is rapidly absorbed and distributed and about 10 per cent appears unchanged in the urine. The metabolic fate of the rest is unknown. There is no accumulation. The drug is antihistaminic and anticholinergic, and like chlorpromazine, it potentiates the action of other sedatives and narcotics. Clinically it seems to be more powerful than chlorpromazine in quieting mentally disturbed patients. Manic-depressive patients are especially helped, but chlorpromazine seems better in schizophrenia. Mepazine has many undesired side-actions, as dizziness, nausea, constipation, jaundice, and agranulocytosis. The dose varies from 100 to 400 mg.

Perphenazine (trade mark "Trilafon") is a piperazine derivative of chlorpromazine, and roughly is more potent and less toxic than its parent compound. Its pharmacology and clinical use is similar to chlorpromazine. It is strongly antiemetic, and is helpful in a wide range of mental disturbance at low doses of 4 to 16 mg. daily.

Prochlorperazine (trade name "Compazine") is another piperazine derivative of chlorpromazine, but more potent as an antiemetic and blocker of conditioned

reflexes. It has less adrenergic blocking action, however, and it is antihistaminic. Its toxicity is much less than chlorpromazine. It is more useful in mild emotional disturbances than in severe mental illness. The dosage is 15 to 40 mg. daily.

Diphenyl methane compounds: The two drugs of this type which have come to clinical use as tranquilizers deserve much more extended study than they have received in comparison with many related compounds. As indicated in the structure of benactyzine and hydroxyzine, there is a great variety of similar substances which may show actions highly applicable to clinical conditions where sedation is desired. The range of action now offered by the tranquilizing drugs gives the alert physician an amazing opportunity to select that which will likely be most useful to the particular patient with whom he is concerned. But it is necessary that the comparative details of the pharmacological action of these various drugs be made available to physicians so that they may make intelligent choice of what to use.

Benactyzine (trade name "Suavitil") is the diethylamino-ethyl ester of benzilic acid, and as the hydrochloride is readily soluble in water. It is rapidly absorbed from mucous membranes and is excreted by the kidneys. It has local anesthetic action, and is anticholinergic, with quinidine-like action on the heart. It reduces response to stress, and induces tranquility. It is not useful in psychotics, and only mildly helpful in neurotics. In clinical studies with placebo controls, the effect of benactyzine was not impressive. It gives mild mental relaxation, with some feeling of detachment and some muscle relaxation. The dose is 1 to 3 mg. daily.

Hydroxyzine (trade name "Atarax") is a chlorinated piperazine derivative of diphenylmethand, and as the hydrochloride is soluble in water. It is a mild sedative and relaxant, with antihistaminic and anticholinergic action. It has been helpful in anxious tense patients with emotional disturbances, but it is not useful in psychotic patients. It has been successfully used in anxiety states in children, and in some cases of emotional dermatoses. The dose is 25 mg. thrice daily.

Central Nervous System Relaxants: Quite similar to the mild effects of the diphenyl methane tranquilizers are the actions of the chemically unrelated relaxants meprobamate, phenaglycodol, ectylurea, and azocyclonol. Lacking detailed information on the mechanism of action of these compounds it is impossible to suggest what factors in their chemical composition is responsible for their action. Their actions seem to be sufficiently different to indicate that they probably do not act in a similar way. The net clinical effect, however, is similar.

Meprobamate (trade names "Miltown," "Equinil") is an alkyl propanediol, related to mephanesin, the potent muscle relaxant. It is a white bitter powder slightly soluble in water. The pharmacological properties of meprobamate were thoroughly studied by Berger, who had introduced mephanesin. Meprobamate is readily absorbed from mucous membranes, and is conjugated with glycuronic acid to be excreted in the urine. In addition to relaxing skeletal muscle, it antagonizes convulsants and depresses multineuronal reflexes. Its action is to block thalamic-cortical circuits, and reduce mid-brain functional activity, as

indicated electrically. Clinically meprobamate is widely used, and its low toxicity and infrequent untoward reactions, with its definite tranquilizing effects, suggest a broad range of helpful indications. It is particularly helpful in anxiety syndromes, in chronic psychiatric patients, muscle disorders, and hypertension. It is not satisfactory in schizophrenia. With anticholinergic agents, it is used to relieve peptic ulcer. There may be occasional skin rashes from its use, with drowsiness, and mild intestinal malaise. The dose is 400 mg. daily.

Phenaglycodol (trade name "Ultran") is also a diol, but is a chlorphenyl compound, which appears as a white water-insoluble powder. Gibson and his associates noted its marked anticonvulsive and sedative action in comparison with a large number of other butane-diols. With low toxicity it reduces spontaneous activity, depressing multi-neuronal pathways, in the same way as meprobamate. Clinically it is useful in anxiety syndromes, and brings emotional relaxation in tense and emotionally-disturbed patients. This occurs without interference with alertness or performance tests. It has no value in psychotic states. Its dose is 300 mg. orally.

Azocyclonol (trade name "Frenquel") is a piperidyl diphenyl carbinol compound, which is a central depressant drug, while its isomer, piprodrol, is a central stimulant. These drugs really deserve much detailed pharmacological analysis in order to try to find what factors cause their marked difference in action when they are so closely allied chemically. Azocyclonol is rapidly absorbed from mucous membranes, but its fate in the body is unknown. Fabing and Hawkins found that this compound antagonizes the hallucinogenic action of lysergic acid diethyl amide (LSD), and Rinaldo and Himwich noted that it prevents the EGG pattern of mescaline and LSD. However, it does not antagonize the stimulating effect either of amphetamine or of its isomer, piprodrol. Clinically azocyclonol is useful in the dissociation syndromes of schizophrenia. It is very safe, and no toxic or undesired side-actions have been reported. Cohen recommends its use with chlorpromazine and reserpine in mental confusion and severe schizophrenia. The dosage is around 25 to 50 mg.

Ectylurea (trade name "Nostyn") is ethyl-crotonyl-urea, a white crystalline powder insoluble in water. It is promptly absorbed from mucous membranes, and Crandall showed that more than three-fourths is excreted as urea, with about 10 per cent unchanged. Ectylurea is mildly sedative, and probably acts as a urea-type depressant. It has low toxicity and no significant effects on cardiovascular or respiratory functions. It is neither anticonvulsant nor analgesic. Clinically it is a mild tranquilizer in tense and anxious patients. It has no value in acute or chronic schizophrenia. The dose is 200 mg. thrice daily.

New Central Nervous System Stimulants

The new central nervous system stimulating drugs greatly broaden the range of useful and relatively non-toxic drugs which physicians can employ in extension of the long-used caffeines, strychnine, metrazol, nikethamide and picro toxin. The caffeines are mild and non-toxic stimulants, but the others may involve many toxic reactions and accordingly are used chiefly in emergency or

specific conditions. The new stimulants are a diverse chemical group, amphetamines, methyl-phenidate and pipradrol. They are all quite non-toxic, and are very useful in various depressed conditions. Nalorphine is a specific narcotic-blocking agent, useful in combating the effects of morphine or its derivatives.

The amphetamines have developed from the studies of Alles, and include amphetamine, dextro-amphetamine, and methyl amphetamine. They are white crystalline substances whose salts are soluble in water. Rapidly absorbed from mucous membranes, they are metabolized by hydroxylation on the ring, and maybe by the action of amine oxidases. They are not cumulative, and only slight tolerance develops on long administration. They activate the reticular alerting system, have some analgesic action, and greatly reduce fatigue and appetite, and promote wakefulness. Clinically they are used in a great variety of conditions from the specific treatment of narcolepsy to the management of obesity. Tainter has shown the specially marked central stimulating effect of the dextro of amphetamine, and this is available as "Dexedrine." Although abused as "pep pills for thrills," the amphetamines are not addictive. They are sympathomimetic in their peripheral actions, tending to cause vasoconstriction and broncho-dilation. Their dosage is from 5 to 20 mg. orally.

Methyl-phenedate (trade name "Ritalin") is methyl-phenyl-2-piperidine acetate, dispensed as the hydrochloride, which is water soluble. It is rapidly absorbed from mucous membranes and appears to be rapidly destroyed in or removed from the body. It causes a marked increase in spontaneous activity, counteracts respiratory depression, and is analeptic against barbitals. It is relatively non-toxic, and while increasing renal excretion of water, has no effect on cardiovascular functions. Clinically it is helpful in improving catatonic psychotic patients, and has a mild effect against sluggishness and depression. It is helpful in counteracting the depression caused by tranquilizers, and may be used with antihistaminics to prevent drowsiness. The dose is around 5 mg.

Pipradrol (trade name "Meretran") is an isomer of the benzhydrol azocyclonol, which is a mild depressant. Pipradrol, however, is mildly stimulating to the central nervous system. These two drugs should be carefully studied to determine what causes the opposing character of their action, when they are so closely related chemically - pipradrol being the 2-piperidyl derivative, while azocyclonol is the 4-piperidyl isomer. Pipradrol was found by Rinaldi and Himwich to activate the upper reticular alerting system, without, however, causing any stimulation of the inhibitory food-intake center as Broback showed in the case of dextro-amphetamine. The EEG is altered by faster frequency and lower amplitude as in increased alertness. Clinically the drug is useful in depressive state, and in non-deluded schizophrenics. However, it increases anxiety, although it promotes work capacity and ability to concentrate. It is quite non-toxic, and no untoward effects are reported from doses ranging from 5 to 100 mg. daily.

Nalorphine (trade name "Nalline") is N-allyl-normorphine, and was studied by Hart and McCawley on the basis that the irritating effect of the allyl radicle might reduce the respiratory depression common to morphine. It was found that it antagonizes respiratory depression, is not analgesic, and has no constipating action. It probably acts by competitive blocking of receptor sites of morphine or other respiratory depressants on the cells of the respiratory center, allowing

full sensitivity to carbon-dioxide or low oxygen. Clinically it is very useful in antagonizing respiratory depression caused by a variety of drugs and conditions. The dose is 5 to 10 mg. intravenously in emergencies. It seems to be a potent direct respiratory stimulant.

Iproniazid (trade name "Marsilid") is 1-isonicotinyl-2-isopropyl hydrazine, and deserves comment here as a "psychic energizer." It was found to be a potent inhibitor of amine oxidase, and a remarkably effective agent against the tubercle bacterium (not as effective, however, in the chemotherapy of tuberculosis as isonicotinic acid hydrazide, isoniazid). Its marked effect in improving the mental attitude of tuberculosis patients led to the study of iproniazid in mental disorder. It was found by Udenfriend and his associates that it prevents loss of serotonin from the cells of the mid-brain, and thus has an action opposite to that of reserpine. This action probably results from its inhibition of amine oxidase. Clinically it is useful in managing mild depressions, and stimulates appetite. Its action is gradual and not dramatic. It may cause dizziness, constipation, and sweating. The dosage is 50 mg. thrice daily.

New Drugs Against Motion Sickness

Motion sickness seems to result from conditioned reflexes established in the brain stem as a result of sensory stimuli from the labyrinth associated with unusual body motion, so that autonomic reflexes of nausea, vomiting, sweating, and dizziness occur. Scopolamine, which blocks brain stem reflex pathways, has been used to antagonize motion sickness, but its action is not satisfactory. Gay and Carliner noted the effectiveness of certain antihistaminics against motion sickness in 1949, and now several new ones are available, including dimenhydrinate, cyclizine, promethazine, and meclizine. These have been well surveyed by Chinn.

Dimenhydrinate (trade name "Dramamine") is a chlorinated theophylline derivative of the antihistaminic diphenhydramine (trade name "Benadryl"), which is more antihistaminic than duphenhydramine, but less spasmolytic. Its antiemetic effect is largely due to its diphenhydramine content. It has low toxicity and has atropine-like anticholinergic actions. It also causes drowsiness. This is its chief trouble in preventing motion sickness. It is effective as an antiemetic in many other conditions, as in nausea of pregnancy and in postanesthetic nausea. The dose is 50 to 100 mg. orally.

Cyclizine (trade name "Marezine") is diphenylmethyl-4-methyl-piperazine, and is an antihistaminic acting much like dimenhydrinate. It reduces reflex responses to labyrinthine stimuli, and it is relatively free from many of the undesired effects of antihistaminics, such as drowsiness. The dose is 50 mg. thrice daily by mouth for the prevention or management of nausea and vomiting.

Promethazine (trade name "Phenergan") is a phenathiazine antihistaminic, which has been widely used in relief from allergic conditions. It has long action, with central nervous system depression of a mild sort. It has been found useful clinically in many conditions where nausea and vomiting are involved. With relatively low toxicity, it has wide use by physicians. The dose for control of motion sickness is 10 to 25 mg. orally.

Meclizine (trade name "Bonamine") is chlorbenzhydryl-4-methyl-benzyl-piperazine, and is a long-acting antihistaminic and mild central depressant. It is not clear whether its effect against motion sickness is due to its antihistamine action or to its central depressant effect. At any rate, it is widely and successfully used in preventing and treating motion sickness or nausea and vomiting. Like other drugs used against motion sickness it may interfere with alertness and attentiveness, so that patients who take it should not try to handle machines or to drive automobiles. These depressant effects may be counteracted by dextro-amphetamine. In treating the nausea of pregnancy the antiemetic drugs may be helpfully combined with pyriodoxine. The dose of meclizine is 25 to 50 mg. orally.

Summary

A rich variety of new drugs are available for modifying mood and behavior. From their careful study may come much information on the complicated manner in which our central nervous systems function. This knowledge would be valuable in determining the mechanisms of action of these new drugs and of old ones also, so that physicians would be able to choose intelligently what particular drug might be suited to purpose desired in individual patients.

Already it is clear that many physiological and biochemical factors are involved, the functions of which ramify over the whole body. This is to be expected with the central nervous system exercising the major coordination of bodily activity in relation to the environment. It includes the exceedingly complex organization and operation of the whole nervous system, with its regulatory feed-back, and its highly efficient timing for adjustment and adaptation to changing conditions. It includes the important viscero-cortical interrelationships which the Russians are exploring so energetically. There is the complex endocrine system for prompt and sustained response to acute or maintained stress, based on the pituitary-adrenal hook-up and its nervous connections. There is also the complex of intracellular and extracellular metabolic cycle with its quick chemical control of nerve conduction and synaptic transmission, with the dawning realization of the relations between the mid-brain and the autonomic nervous systems. Through all of this is beginning to appear the probabilities of disturbed metabolic factors, in addition to derangements of nervous pathways, which may be at the bottom of various mental disorders.

The new tranquilizers, the new central nervous stimulants, the hallucinogenic compounds, and the antihistaminics give promise of much empirical usefulness in handling many aspects of mental disturbance, which were not apparent a few years ago. However, most of these new drugs pose disciplinary problems for physicians. How may one fairly judge between the competing claims made so alluringly for these various new drugs? Fortunately, they are relatively nontoxic, so that patients may easily be protected against their untoward effects. Luckily also, the high sense of responsibility of the pharmaceutical manufacturers who put them out assures reasonable statement of claims about their value, and reasonable data on their actions. Physicians are also protected by the careful regulations of the Food and Drug Administration, and by the appraisal of the Committee on Drugs of the American Medical Association. But the duplication of

names is unfortunate: every one of these new drugs has two or more names; one is the public name open to all to use, and employed for designation in the U.S. Pharmacopeia or in New and Non-Official Remedies, while the others are trade names used in advertising. Physicians should use the public names, and discipline themselves to do so always. If a particular brand is desired, then name the company making that brand. The trouble here is that manufacturers may so drum into consciousness the trade name that it sticks even after patent rights expire, and then higher prices may be obtained for it than is warranted under competitive conditions. Further, the advertising, even in professional journals, shows a tendency to flamboyance and allure that is unseemly in the interest of economy and scientific information. If manufacturers would give more scientific data in their professional ads, and use their own names to specify new drugs by public name, there would be little room for any complaint.

Physicians and pharmacists by exercising self-discipline in using only public names of new drugs can help manufacturers to be more seemly about the whole matter of introducing new drugs. But the test of the situation is the result: the treatment of mental disorder is vastly improved, and may be expected to get better all the time, and for this we all owe a great debt of gratitude to the pharmaceutical industry which has researched the problem and given us such a wealth of new drugs which can be used with success in so many cases where it is desired to alter mood and behavior into acceptable social ways.

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CURRENT CONCEPTS IN THE BIOCHEMISTRY OF MENTAL DISEASE

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The contributions of biochemistry to the fields of psychopharmacology and psychiatry have been outstanding in the past several years. Some of the findings have been of such significance that the concept of a biochemical origin of mental disease now receives serious consideration.

Perhaps the greatest single factor leading to this change in concept was the discovery of the psychotomimetic agent, lysergic acid diethylamide (LSD), a semi-synthetic derivative of the ergot. In minute doses LSD is capable of producing marked and bizarre alterations in the behavior of man. Many other substances which are capable of producing mental symptoms have been known prior to LSD. These drugs, however, frequently exhibited the mental effects only when the doses of the drugs were raised to toxic or near-toxic levels. LSD, on the other hand, was effective in doses as small as 25 - 30 micrograms, equal to something like 0.5 microgm/kgm of body weight. It has been calculated recently by Axelrod that with the doses of LSD used it would require something in the neighborhood of 0.0003 microgm/gm of brain tissue to produce the hallucinogenic effects. Since such small quantities of LSD were needed for the effects, some investigators even considered the possibility of the abnormal formation of LSD or LSD-like substances by the body, thus producing the schizophrenic state.

The discovery of LSD has reopened studies of the other previously known psychotomimetic agents in an attempt to better understand the drug induced psychoses. When the various psychotomimetics were compared, it was found that many of them, but not all, possessed certain structural similarities, namely the indole nucleus. Among those possessing this nucleus was bufotenine, harmine, adrenochrome and adrenolutin. LSD also belongs to this group of drugs since the lysergic acid mostly possesses the indole nucleus. This fact has led many investigators to seek for substances possessing indole structures in the blood and urine of schizophrenic patients.

Mental disease may arise through the alterations of metabolic processes necessary for normal brain functions. Such alterations may be of qualitative or a quantitative nature; for example:

1. The overproduction of some normal metabolite which causes an imbalance of brain function, leading to the mental alterations.

2. The lack or deficient production of a normal metabolite necessary for proper brain function. This lack may lead to an imbalance and mental alterations.

3. The production of some abnormal metabolite which is capable of producing the abnormal mental states.

Instead of the word "production" we may substitute the word "liberation" in the above statements since it is possible that production may proceed at normal rates but the rate of liberation of such substances from a stored form may become altered.

Keeping the above approaches to the concept of mental illness in mind, we may proceed to the current ideas on the genesis of the schizophrenic states. At present there seem to be three main biochemical views on the cause of mental illness. These may be classified as follows:

1. Abnormal Tryptophan Metabolism
2. Abnormal Epinephrine Metabolism
3. Ceruloplasm and Taraxein

Of these three, the first, abnormal tryptophan metabolism, has received the greatest amount of consideration by those working in the biochemistry of mental disease.

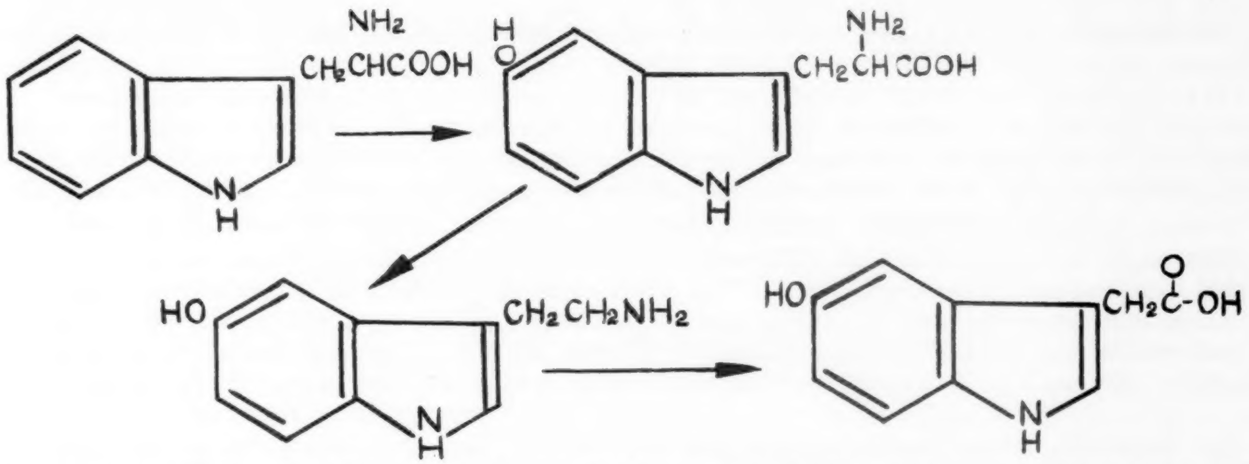
Abnormal Tryptophan Metabolism

At the recent conference in Vancouver, B. C. on the Biochemistry of Mental Disease, about one-half of the time was devoted to subjects concerned with the abnormal indoles in the bloods and urines of schizophrenics. A large part of the indoles in the body arises from the metabolism of the amino acid tryptophan. Tryptophan undergoes a number of complex metabolic processes in its transformation to other substances. In regards to the biochemistry of mental disease we are especially interested in the formation of 5-hydroxytryptophan (5HP) and 5-hydroxytryptamine (serotonin, 5HT) from tryptophan since 5HT has become recognized as a naturally occurring amine and possibly possessing central nervous system actions. We shall therefore direct our attention to the metabolism of tryptophan at the level of its hydroxylation and decarboxylation. It should be kept in mind, however, that in schizophrenia or other mental illnesses there may be defective metabolism in the other pathways of tryptophan breakdown, but these are not as well understood at the present time as the 5HTP-serotonin pathways.

The Role of Serotonin in Brain Function

Serotonin, or 5HT, is the decarboxylation product of the amino acid 5HTP. 5HTP arises from the better known amino acid tryptophan through a hydroxylation process. Approximately 3 per cent of the total tryptophan passes through the serotonin pathway. Serotonin in turn is metabolized rapidly by the enzyme monoamine oxidase.

Serotonin is a recent addition to the family of biological amines to be found in mammalian tissues. Its presence in other invertebrate and vertebrate forms has also been confirmed. In the mammal, serotonin is found in relatively high concentrations in the gastro-intestinal tract, the blood platelets and in certain areas of the brain. Pharmacologically it possesses a marked smooth muscle stimulating action which is antagonized by a variety of drugs, among



them being LSD. Woolley as well as Gaddum found that very small quantities of LSD were quite effective in blocking the serotonin-induced contractions in gut and uterine musculature. This specific antiserotonin action of LSD led these authors to postulate the possibility that a similar effect might be exerted by LSD in the brain to produce the aberrant behavioral effects in man. According to these authors LSD might be able to block the normal actions of HT in the brain, thus causing in effect, a serotonin deficiency. This indicated that serotonin was an important substance for normal behavior and that schizophrenia might be caused by a defect in HT metabolism, i.e., due to its deficiency. These suggestions probably contributed largely to the investigations in the metabolism of serotonin, giving us the presently available knowledge in this phase of tryptophan metabolism.

Subsequent studies of these agents revealed that LSD not only blocked the actions of serotonin, but in addition, possessed serotonin-like activity in a number of experimental preparations. These results, as well as the fact that certain other specific antiserotonin drugs, especially BOL (the bromine analogue of LSD) did not produce the LSD-like psychotomimetic actions but brought out the possibility that instead of blocking serotonin, LSD might produce its psychic actions by mimicking the actions of large quantities of HT in the brain. Schizophrenia, according to such a hypothesis, would be the result of an overabundance of HT in the brain.

The possibility that HT did play a role in brain function was strengthened by the findings of Brodie, et al. In studying the tranquilizing actions of reserpine they found that there were certain properties shared by both this compound and serotonin. For example, both agents potentiate the sleeping time of various anesthetics, this block is reversed by LSD, and both have structural similarities. It seemed that the reserpine action could be explained by serotonin release. The experiments that followed showed that reserpine was indeed capable of releasing serotonin from the brain and other tissues. With these and other evidences, Brodie, et al., proposed a mechanism of action for the tranquilizing effects of reserpine, basing it on the release of serotonin from the brain. The hypothesis may be summarized as follows:

Serotonin is found in the brain in a bound form. In this bound state it is neither active nor attacked by monoamine oxidase. Under normal physiological

conditions a certain amount of serotonin is released in order to maintain normal brain function. Reserpine in some manner destroys or inactivates the binding sites causing the bound serotonin to be released, thus decreasing the normal levels of brain serotonin. The process of serotonin formation continues, however, and since binding or storage is no longer possible, there is a constantly high concentration of free serotonin exerting its sedative action in the brain. The tranquilizing or sedative action of reserpine, according to Brodie, is due to this high concentration of free serotonin in the brain, and this persists until the binding sites are restored. He also explains the long duration of action of reserpine as being due to the relatively long period of time required for the restoration of the binding sites. His data is supported by the fact that the action of reserpine lasts far beyond the duration of the drug in the body.

From his studies with reserpine and serotonin, Brodie has also postulated as to the significance of serotonin in the brain and its possible role as a neurohumoral mediator of the central nervous system. The proposal has been made that in the central nervous system, norepinephrine could be the mediator of the sympathetic division, while serotonin could be the mediator of the parasympathetic division. Under normal conditions a balance exists between the two divisions. Reserpine causes the imbalance to result by destroying the serotonin binding sites and flooding the centers with free HT, resulting in the overactivity of the parasympathetic system. Since the proposals were made it has been found that not only serotonin but also norepinephrine is released from its binding sites, thus causing a fall in brain norepinephrine as well. This finding has again raised the question of the role of serotonin in the reserpine action.

In order to understand the role of serotonin in the brain several groups of workers are interested in the area of the biosyntheses and destruction of serotonin by the enzymes 5HTP decarboxylase and monoamine oxidase, respectively. By finding a specific 5HTP decarboxylase inhibitor which is effective _in vivo_, it would be possible to determine the central manifestations of serotonin deficiency. Likewise, by using a specific monoamine oxidase inhibitor, it would be possible to determine the effects of high brain levels of serotonin. The first of these approaches, i.e., the inhibition of 5HTP decarboxylase has not yet been accomplished in a specific manner. The inhibition of monoamine oxidase on the other hand has received considerable attention in the studies of serotonin. The drug most extensively studied has been isopropyl-isonicotinic acid hydrazide, better known as iproniazid or "Marsilid." This drug was earlier used as an anti-tubercular agent, but because of its side actions, its use for this purpose was discontinued. The chief disadvantage of iproniazid is its central excitatory effects, even producing psychotic actions after repeated or prolonged administration. Iproniazid was subsequently found to be a potent monoamine oxidase inhibitor which was effective _in vivo_. The administration of iproniazid to animals shows a marked increase in the levels of 5HT, indicating that the free serotonin was not undergoing the usual rate of breakdown, thus causing serotonin levels to increase. When brain serotonin levels rise sufficiently there is a change in the behavior of the animal as characterized by central nervous system excitation which is not unlike that seen with LSD. This is also seen with the administration of the serotonin precursor, 5HTP. If 5HTP is given after iproniazid this excitation is produced with much smaller amounts of the amino acid. Here it is presumed that the amino acid precursor is being decarboxylated to form serotonin, but

destruction of the amine is inhibited by iproniazid, resulting in a rapid increase in brain serotonin.

Another method to increase the levels of free serotonin in brain is by the administration of reserpine. As mentioned earlier, reserpine releases the bound form of serotonin, thus causing an increase in its free form. Under normal conditions this free serotonin is rapidly deaminated by monoamine oxidase. If iproniazid is given prior to reserpine administration, the released serotonin is not destroyed but persists to exert its action. Under such conditions the usual reserpine effects of tranquilization and sedation are absent; rather, there is a state of excitation which again resembles the LSD response and in many respects is opposite to the usual reserpine effects. These results indicate then that the changes in brain serotonin levels correlate with changes in behavior. A low serotonin level produces depression and sedation, while high levels produce excitation and hyperactivity.

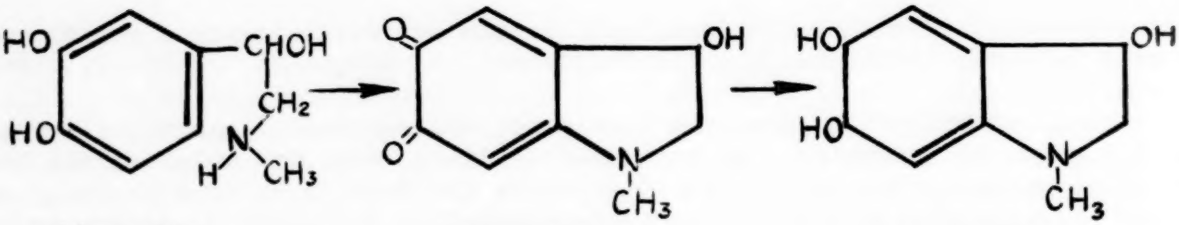
The recent findings that iproniazid was an effective "psychic energizer" or a "resurgitive" is based on these findings. The Rockland State Hospital group, seeing that iproniazid produced the state of central nervous system stimulation by its serotonin protective ability, administered it to some of their depressed mental patients. Iproniazid produced a marked improvement in the mood and behavior in a good percentage of the depressed patients.

This mass of information on serotonin has been compiled only in the last few years. Whether serotonin is involved in the schizophrenic state has, however, not been established. At any rate the data suggest that it may have a role in normal brain function.

Epinephrine Metabolism and Its Relationship to Mental Disease

About five years ago a group of workers in Canada reported on the hallucinogenic properties of adrenochrome administration in man. The response so resembled the psychotic state in schizophrenia that they postulated an abnormal metabolism of epinephrine as the cause of the disorder. Adrenochrome is the breakdown product of epinephrine and possesses the following structure. It is formed by the oxidation of epinephrine to form the quinone.

Adrenochrome by itself is an unstable quinone, but can be made quite stable by forming the monoxime or the semicarbazide. When these stable derivatives of adrenochrome were given to human volunteers no psychic changes could be observed. Apparently the unstable form of adrenochrome was necessary for the production of the abnormal behavior effects. Since these stable forms were not effective it was suggested that possibly adrenochrome itself was not the active agent but that an agent which was another metabolite of epinephrine might be responsible for the psychic effect. This led to the study of adrenolutin, another indole compound which represents another metabolic product of epinephrine past the adrenochrome stage. Both adrenochrome and adrenolutin are therefore considered as psychotomimetic drugs and may play a role in the genesis of the schizophrenic state. The main drawback to their participating in the disease is the fact that neither of these substances have been found to occur in the body. They may exist



Adrenalin Adrenochrome Adrenolutin

biologically, but because of their instability, and the lack of a sensitive test they are not detectable at the present time.

Hoffer, et al., therefore have postulated that the psychotic state in schizophrenia may be developed by the abnormal metabolism of epinephrine. Instead of being detoxified in the normal manner it may undergo oxidation to form adrenochrome and adrenolutin. He supports his hypothesis by pointing to the many potential pathways by which adrenochrome and adrenolutin formation can take place in the tissues and blood. He has also compared the biochemical and physiological activities of adrenochrome with the schizophrenic state and has found many similarities. Thus far, however, the picture of an abnormal epinephrine metabolism in the genesis of schizophrenia is not very clear.

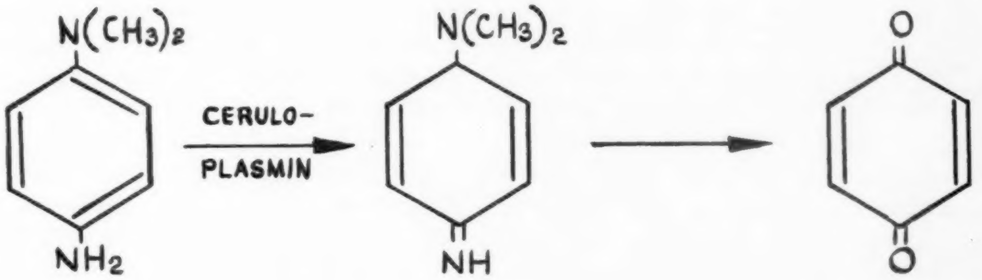
Ceruloplasmin and Taraxein

The most recent addition to the biochemical concepts of mental disease was presented by Heath and co-workers at Tulane University. They administered extracts of sera from schizophrenic patients to human volunteers and found that the typical symptoms of the schizophrenic state could be produced. This was probably the first instance of demonstrating that the schizophrenic's blood contained some substance which was active in producing symptoms of schizophrenia. Earlier attempts had shown that schizophrenic sera or urines did contain substances which were toxic to tissue cultures or to the growth of plant seedlings, but nothing had indicated them to be of a psychotomimetic nature. Heath and his group are continuing their investigations of this substance and have given it the name of "Taraxein." Taraxein then, according to these workers, is the active psychotomimetic substance and is produced in the body. Neither the nature nor the metabolic pathways of this substance are known. In the recent meetings of the American Psychiatric Association the Tulane group reported more data on the effects of Taraxein in normal patients as well as to remitted schizophrenic patients. It appears that with the latter group of subjects Taraxein had a much more pronounced effect than in normals.

In the course of their studies on the biochemical alterations in schizophrenics, Heath's group also considered the enzymes associated with epinephrine metabolism. Since earlier reports indicated a rise in serum copper in schizophrenics, they determined the activity of ceruloplasmin, a copper containing enzyme in serum. Ceruloplasmin is capable of oxidizing epinephrine at rather a slow rate. In the schizophrenic the ceruloplasmin activity is considerably

greater than in normals, suggesting that the degradation of epinephrine proceeds by this pathway in larger quantities in the schizophrenic. By incubating epinephrine with plasma from schizophrenic patients, Leach found that a much greater quantity of epinephrine is oxidized than in normal plasma. This increased activity, however, was not specific for only schizophrenic plasma, since plasma obtained from patients with certain other diseases and without abnormal behavior also showed the increased oxidation of epinephrine. He also found that not only epinephrine, but also adrenochrome, was rapidly oxidized by the serum, giving some support to the work of Hoffer, et al. Hoffer, who had earlier postulated on the role of adrenochrome and adrenolutin as the psychotomimetic factor in schizophrenia, using the identical method, confirmed the oxidative powers of schizophrenic serum. He has therefore suggested that this substance was the final active material in the abnormal metabolism of epinephrine.

In connection with ceruloplasmin the recent report by Akerfeldt on a chemical test which would diagnose schizophrenia has received considerable attention. The Akerfeldt test consists of incubating a sample of serum with a solution of p-phenylene diamine or N,N-dimethyl phenylene diamine. Akerfeldt found that the sera from schizophrenic patients possessed the ability to oxidize these compounds resulting in the formation of a deep red color. Normal sera was much less effective in showing this reaction. A study of this phenomenon showed that the oxidation of these chemical compounds was accomplished by the ceruloplasmin in the sera. The conversion of the p-phenylene diamine on N,N-dimethyl phenylene diamine appears to proceed through the formation of an unstable imine intermediate which is further oxidized to form a quinone. The quinone is responsible for the color of the reaction.



Since sera from schizophrenic patients shows a greater rapidity in producing this red reaction, it is an indication of a greater activity of the ceruloplasmin. Approximately 70 - 80 per cent of the acute schizophrenics exhibit a positive Akerfeldt test, and its possibility as a diagnostic test for schizophrenia has been considered. This test, however, has been found to show a positive reaction in a good percentage of several other disease states, e.g., terminal carcinoma, pregnancy, thrumatic heart disease, among others. Because of its relatively nonspecific nature Akerfeldt himself does not consider this test to be adequate as a diagnostic tool by itself for schizophrenia. Rather than a method for diagnosis, the findings of Akerfeldt are important in indicating the presence of an abnormal biochemical function in the schizophrenic, thus supporting the view that this disease may be of a biochemical origin.

THE PHARMACOLOGICAL APPROACH TO MENTAL ILLNESS*

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Psychotomimetic and psychotherapeutic drugs have opened a new line of approach to the field of mental disease and health. With each new advance, problems arise making it essential that all avenues of approach be utilized in ascertaining the possible sites of drug action. This is of particular importance insofar as the brain is concerned, because of the vital centers which can be affected. Also of importance is the amount of drug required to produce a particular effect and the possibility that the blood-brain barrier may prevent the entrance of, or hasten the exit of drugs effectively decreasing the possibility of direct drug action in the brain. The use of the implanted cannulae developed by Feldberg and Sherwood (1953) and Haley and Dickinson (1956), allows the investigator to introduce directly into the ventricular spaces of the brain known concentrations of drug, and to study the centrally-induced effects without having to wait for drug transport and penetration of the blood-brain barrier to take place. More than forty drugs have been studied by this technique, but the present discussion will concern itself only with those drugs which are considered to be psychotomimetic or psychotherapeutic in action. Furthermore, an attempt will be made to correlate the various effects observed with possible central sites of drug action. In this regard it must be borne in mind that exact localization of the site or area of attachment of drug to receptor is not certain because, as Figure 1 shows, the drug will mix with the cerebro-spinal fluid and be carried throughout the brain ventricles.

Psychotomimetic Drugs

Lysergic Acid Diethylamide (LSD-25): In dogs intraventricular injection of 20 to 140 µg caused the following symptoms within one to five minutes: whining, shaking of the head, salivation, retching, emesis, micturition, tachypnea, mydriasis with reactive pupils and ataxia. Recovery appeared to occur after 15 to 20 minutes but the animals barked for several hours after the other symptoms were gone. The most striking effect was a reversion to a puppy-behavior pattern. Throughout the acute period, the animals appeared frightened, but there was no impairment of their ability to perform simple tasks or commands (Haley and McCormick, 1956). Haley and Dasgupta (1956) observed a similar pattern of fear in cats receiving 37.5 to 210 µg. of LSD, but the responses of the

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cat appear to be predicated upon the emotional state of the animal prior to drug injection. In animals already somewhat fearful, the fear response was accentuated. The cats were also extremely sensitive to both sound and light, and at times to touch. The autonomic effects seen included mydriasis with both reactive and non-reactive pupils, sweating of the foot pads, micturition, salivation and defecation. Sturtevant and Drill (1956) obtained similar results and also reported catatonia and depression. Haley and Dasgupta (1956) saw the depressive state, but believe it to be related to the pre-injection state of the particular animal. Naturally, prior emotional state of the animal would not be involved in the sham rage phenomena seen by Gaddum and Vogt (1956) after administration of 800 μg of LSD. In all probability such a response is nonspecific, being related to chemical toxicity because it was also produced by morphine.

Knowing the above behavioral changes and evidences of autonomic nervous system discharge, it is logical to question the role of the brain in the various phenomena observed. This is of particular importance because Haley and Rutschmann (1957) found only 8-10 per cent of the dose of LSD in the brain of cats ten minutes after injection although drug effects were still present. This indicates a high efficiency of the blood-brain barrier in removing LSD from contact with vital brain areas and the extremely low concentrations of drug required to cause profound temporary changes in central nervous system activity. The problem has been approached by measuring changes in electrical and enzymatic activity of the brain.

Bradley (1953) and Bradley and Elkes (1953) related the alerting behavior and alerting type EEG response of cats after intracerebral LSD to mesencephalic and spinal connections. While Schwartz et al (1956) correlated drowsiness from intracerebral LSD with occasional slow waves in the EEG, Killam and Killam (1956) reported that LSD increased the duration of rhinencephalic seizures with out an increase in threshold. Marrazzi and Hart (1955) showed that LSD inhibited the cortical terminal synapses of the transcallosal pathway in the cat brain. Purpura (1956) reported that low doses of LSD produced facilitation of the evoked auditory and visual primary responses in the cat. Higher doses depressed the auditory responses but continued to facilitate the visual ones. The results of these investigators can be correlated with the auditory and visual responses seen in cats after intracerebral injection. LSD has a dual action, exciting specific afferent systems and inhibiting nonspecific and corticocortical systems. Purpura (1956) has proposed that LSD facilitates axosomatic synapses and inhibits axo-dendritic synapses possibly due to differences in the bioelectrical properties of dendrites and cell bodies. Perhaps the synaptically excitable membrane components of apical dendrites are also differentially affected by LSD. The effects of LSD on receptor or cell membranes may be one of the reasons for its prolonged action at such low concentrations. Intracerebral LSD reduces or abolishes pressor responses from carotid occlusion, asphyxia, etc., indicating that central vasomotor areas are susceptible to its effects (Ginzel, 1955). In all of these aspects, it appears that the higher integrating centers and nervous pathways are influenced by LSD. Whether the actions are directly on the nervous elements or indirectly on them by modification of brain enzymes systems cannot be stated for certain, but it is known that both are affected.

Clark, et al. (1954) reported that succinic dehydrogenase was moderately inhibited while cytochrome C oxidase was stimulated by LSD. Lewis and McIlwain

(1954) observed that LSD inhibited respiration and glycolysis in isolated cerebral cortex slices after electrical stimulation. Such effects on brain respiration and metabolism are important but inhibition or stimulation of enzymes involved in nervous transmission may be of greater importance in explaining the central actions of LSD. Poloni and Maffezzoni (1952) correlated increased acetylcholine in the cerebral cortex with catatonia and excitation. Thompson et al. (1954, 1955) showed that true cholinesterase was unaffected by LSD, but psuedocholinesterase was inhibited, and the latter effect was readily reversible. This may be part of the explanation of the reversibility of the central effects of LSD. Further evidence of the possible involvement of cholinesterase inhibition and the persistence of acetylcholine in the higher centers in the central actions of LSD may be obtained from the work of Feldberg and Sherwood (1954). They observed catatonia in cats after intracerebral injection of large doses of acetylcholine or small doses of eserine or diisopropylfluorophosphate in cats.

Mescaline: After 0.3-15 mg. of mescaline intracerebrally in cats, Schwartz, et al. (1956) observed howling, defecation, mydriasis and scratching. Sturtevant and Drill (1956) obtained similar effects, but no scratching at doses of 1-3 mg. Additional effects included salivation, tachypnea, lacrimation, micturition, retching, ataxia and catatonia. The absence of scratching may have been related to the purity of the drug because commercial mescaline contains a contaminant which produces this effect.

Changes in the EEG following mescaline were reported by Schwartz, et al. (1956). Paroxysms of 10 cps. spikes occurred asymmetrically in the brain and spread to homologous areas. Marrazzi and Hart (1955) found that mescaline had the same inhibitory effect on the cortical terminal synapses of the transcallosal pathway of the cat as LSD. Further neuropharmacological investigation is necessary to determine the similarities and dissimilarities between the various central sites of action of mescaline and LSD. However, it is known that the latter compound is effective at much lower concentrations than the former. This is also evident in enzymatic studies.

Mescaline does not affect either cytochrome C oxidase or succinic dehydrogenase (Clark, et al., 1954). Its inhibitory action on brain respiration and glycolysis, although equal to LSD, required almost twice the concentration to be effective (Lewis and McIlwain, 1954).

5-Hydroxytryptamine: Feldberg and Sherwood (1954) observed muscular weakness, tachypnea, profuse salivation, head tremors and stupor in cats receiving 75-500 µg of 5-hydroxytryptamine. Similar results have been reported by Gaddum and Vogt (1956), Schwartz et al (1956), and Sturtevant and Drill (1956). These latter investigators also reported mania, clonic convulsions, and opisthotonus after doses of 1.2-1.8 mg. Such actions may not be related to drug activity, but may be simple chemical toxicity manifestations. Studies of the effects of 5-hydroxytryptamine on brain activity are difficult unless the intracerebral or close intra-arterial injection is used for administration, because so little drug seems to pass the blood-brain barrier. Perhaps the rapidity of its destruction or storage prevents it from reaching the brain in high enough concentration to be effective.

Schwartz et al (1956) saw only fast, low voltage activity, consistent with the alerting state in cats receiving intracerebral injections of 75-500 µg of this drug. Inhibition of cortical terminal synapses of the transcallosal pathway in the cat was seen by Marrazzi and Hart (1955). In producing this effect, 5-hydroxytryptamine was 6 to 8 times more potent than LSD. Page and McCubbin (1953) have shown that synaptic transmission in the ciliary ganglion is also inhibited by 5-hydroxytryptamine. There is suggestive evidence that 5-hydroxytryptamine is liberated from the spinal cord during reflex activity (Angelucci, 1956). Further investigation of the effects of this drug on the central nervous system are indicated to ascertain its exact status as a possible neurohormone in impulse transmission or inhibition.

It is a fact that 5-hydroxytryptamine is metabolized by monomine oxidase and inhibition of this enzyme can increase the duration of its central effects (Sjoerdsma et al, 1955). The drug itself can act as an enzyme inhibitor, particularly of 5-hydroxytryptophane decarboxylase, one of the enzymes required for its formation (Gaddum and Giarman, 1956). This enzyme is well distributed in the central nervous system with the exception of the highly vascularized area postrema which contains large amounts of 5-hydroxytryptamine (Gaddum, 1956). Perhaps the duration of the central effects is related to the rate of collection of the drug in this area as well as its excretion by the blood-brain barrier and its enzymetic conversion to 5-hydroxyindole acetic acid.

Psychotherapeutic Drugs

Chlorpromazine: In dogs, intraventricular injection of 10 mg. of chlorpromazine produced analgesia, tranquilization, shivering, mydriasis, tachypnea, defecation, barking, mania and hypothermia. Bradycardia followed by tachycardia and ventricular extrasystoles were also seen. A dose of 2.5 mg. produced only transient tranquilization and electro cardiographic changes (Weinberg and Haley, 1956). Cathala and Pocidalo (1952) obtained similar effects in dogs at higher concentrations of drug. Sturtevant and Drill (1956) administered 1 mg. of chlorpromazine to cats causing nictitating membrane relaxation and mild ataxia. At double the dose, the cats responded with tachypnea, catatonia, and no response to pain stimuli. It is apparent that the centrally induced effects of chlorpromazine are similar in both dogs and cats, but one could ask whether the effects seen are related to the local anesthetic action of the drug. While it is possible that local anesthesia could be involved, it appears unlikely because many of the effects observed are also produced by the cardiac glycosides (Weinberg and Haley, 1955; Melville and Slister, 1956). Furthermore, it does not appear that local anesthesia could be involved in the hypothermic response because it is also observed after intravenous administration. This raises the question of what changes chlorpromazine does produce in the central nervous system.

After studying the effect of chlorpromazine on the EEG, Terzain (1952) concluded that the main central effect was depression of the afferent ascending portion of the reticular formation. Aron (1954) has involved the hypothalmus. These views are supported by the studies of Longo et al (1954) and Killam and Killam (1956). Depression or inhibition of the reticular formation would partially localize the site of action of the drug in producing analgesia and tran-

Chlorpromazine has been shown to inhibit several enzyme systems. Abood (1953) reported chlorpromazine inhibited brain mitochondria formation of energy rich phosphorus compounds. ATP-ase and cytochrome oxidase activity were also inhibited. Bersohn et al (1955) reported that succinic dehydrogenase from brain tissue was inhibited but citrate formation from pyruvate or oxaloacetate was not affected. The relationship of enzyme inhibition to over-all chlorpromazine activity in the intact animal is obscure, but it may be related to the depressant effects of the drug.

Reserpine: Haley (1956) reported that 25-50 µg of reserpine intracerebrally in dogs produced salivation, retching, and emesis. When 310 µg were given, salivation repeated emesis with regurgitation of bile, defecation and slight miosis were observed. Electrocardiographic changes consisted of tachycardia, biphasis or inverted T-wave, and an accentuated P-wave. Haley and Dasgupta (1956) found that cats responded to 18-20 µg of reserpine in one-half hour with relaxation of the nictitating membrane, miosis, narrowing of the palpebral fissure to a slit, squinting in response to light, withdrawal to the darkest corner of the cage, diarrhea, anorexia, tranquilization, and a pronounced generalized depression. Normally aggressive cats became docile, and fearful cats became friendly. Recovery was complete within 24 hours. Lower doses were ineffective and the effects of reserpine could be entirely prevented by continuous auditory stimulation during the first hours after drug administration. Sturtevant and Drill (1956) injected 100 µg of reserpine in cats causing immediate meowing as in pain, mydriasis, defecation, drowsiness, salivation, and generalized tremors. Recovery occurred in two hours, but on the following day, miosis, nictitating membrane relaxation, anorexia, diarrhea, and tranquilization were observed. These delayed symptoms are usually seen after parenteral administration of the drug and may be related to its metabolism and conversion to another compound. It is difficult to reconcile the differences between the reports of Haley and Dasgupta (1956) and Sturtevant and Drill (1956), but the time of appearance of symptoms and the difference in size of dose administered may be the important factors. The immediate symptoms observed by Sturtevant and Drill (1956) are generally associated with nonspecific discharge of the autonomic nervous system, whereas the symptoms seen by Haley and Dasgupta (1956) are generally associated with the known sections of reserpine. Furthermore, it was found that the reserpine metabolites, trimethoxybenzoic acid, reserpic acid and methylreserpate, alone or in combination had no reserpine-like activity following intracerebral injection. Combinations of subthreshold doses of reserpine and 5-hydroxytryptamine also did not duplicate the central effects of reserpine.

Sheppard et al (1955) studied the metabolism of tagged reserpine and found none of the drug in the brain within six hours. This is surprising because available evidence points to an action of reserpine on the brain. The drug leaves the blood stream rapidly and concentrates in fat deposits. Reserpine is hydrolyzed and converted into trimethoxybenzoic acid-like substances. Numeroff et al (1955) also found only traces of reserpine in the brain. Glazko et al (1956) recently reported low levels of reserpine-like compounds in the brain four hours after administration. All of these early studies seem to point to the possibility that reserpine or its degradation products, methylreserpate or trimethoxybenzoic acid, may not be involved in the central effects reported. Recently, however, Plummer et al (1957) and Peets and Schubert (1957) using

reserpine completely tagged with tritium or C^{14} have demonstrated reserpine in the brain 20 minutes after administration and for periods up to 48 hours post-injection. Thus, it begins to appear that reserpine acts *per se* and the quantity required for it to produce pharmacological effects is extremely small. Further experimentation will assist in a more complete solution of the problem.

Electroencephalographic studies by Schneider and Earl (1954) indicate that the tranquilization and unresponsiveness to extraneous stimuli are related to changes in the central regulating mechanisms of the autonomic nervous system in the brain stem. The report by Killam and Killam (1956) points to the central efferent systems of the reticular formation as the site of action of reserpine. Bein et al (1953) believe that sympathetic autonomic areas in the posterior hypothalamus are inhibited by reserpine allowing the parasympathetic areas to produce the effects seen. Schneider's (1955) work on decerebrate cat adds further support to this explanation of the central site of reserpine action.

The effects of reserpine upon brain enzyme systems are not too well known. Rau et al (1955) observed no effect on oxygen consumption of rat brain slices at low concentrations of reserpine and depression at higher concentrations. Claus (1955) found increased brain glycogen after reserpine, while MacLean (1955) observed decreased methionine deposition in the hippocampal area and the limbic system. Much more investigation will be necessary before the effects of reserpine upon brain biochemistry become known.

Discussion

The various pharmacological effects produced by intracerebral injection of drugs in cats and dogs are summarized in Tables I and II. The possible sites of action listed are derived from electrophysiological studies of others and should not be considered as the only sites of action because activation of receptors in the cerebral ventricles may, through interneuronal pathways, cause more distance centers to be affected (Haley 1956). These centers may give rise to the observed effects which are, for the most part, evidence of a profound autonomic nervous system activation (see Table I). Furthermore, it would be inconsistent to insist that certain specific sites in the walls of the ventricles are the only ones being affected because the brain ventricles form a closed system and the drugs eventually will spread throughout the entire system. The possibility of diffusion into the mass of brain tissue surrounding the ventricles must also be considered. The interrelationship of chemical structure to site of action is difficult because so many diverse drugs appear to affect the same areas. However, certain drugs appear to have very specific effects on certain areas (see Table II).

Summary

The effects produced by the introduction of psychotomimetic and psychotherapeutic drugs into the cerebral ventricles have been discussed. The indwelling cannula procedure allows an assessment to be made of the centrally induced effects of drugs in the unanesthetized animal. It has been shown that the non-specific effects produced by this method of administration are related to a

discharge of the autonomic nervous system. Specific drug effects not related to chemical structure can be observed and appear to be evidence for specific activation of known brain centers.

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TABLE I

General Effects After Intracerebral Drug Injection

Pharmacological Effect	Effective Drugs	Possible Central Sites of Action
Salivation	LSD, Mescaline, 5-HT, Reserpine Strophanthin derivatives, Procainamide, Curare, Histamine, Hexamethonium, Decamethonium, Banthine, Atropine, Morphine, Ergonovine.	Pre-optic hypothalamus. Salivatory nuclei of medulla.
Retching	LSD, Mescaline, Reserpine Strophanthin derivatives, 5-HT, Quinidine, Acetylcholine ATP, Adrenaline, Histamine, Hexamethonium.	Brain stem reticular formation.
Emesis	LSD, Reserpine, Strophanthin derivatives, Adrenaline, Hexamethonium, Decamethonium, Banthine, Atropine, Curare, Frenquel, Bulbocapnine.	Chemoreceptor trigger zone of IV ventricle. Caudal portion of diencephalon. Ependymal receptors in lateral ventricle.
Mydriasis	LSD, Reserpine, Mescaline Strophanthin derivatives, Chlorpromazine, Quinidine, Ergonovine.	Posterior hypothalamus. Centers in cerebral cortex and brain stem.
Nystagmus	Strophanthin derivatives, Quinidine, Procainamide, Banthine.	Pontine area or medial Longitudinal fasciculus.
Defecation	LSD, Chlorpromazine, Reserpine, Strophanthin derivatives, Procainamide, Quinidine, Adrenaline, ATP, Histamine, Hexamethonium, Decamethonium, Banthine, Curare, Morphine.	Hypothalamic pre-optic and supra-optic nuclear areas. Medulla oblongata.
Micturition	LSD, Mescaline, Strophanthin derivatives, Quinidine.	Pre-optic hypothalamus. Autonomic centers in diencephalon. Centers in rostral border of hind brain.

(continued)

TABLE I (continued)

Vasoconstriction	Strophanthin derivatives, Quinidine.	Posterior hypothalamus, Vasomotor center in medulla.
Shivering	Chlorpromazine, Strophanthin derivatives.	Posterior hypothalamus
Tachypnea	LSD, 5-HT, Strophanthin derivatives, ATP, Histamine, Hexamethonium, Decamethonium, Banthine, Atropine, Curare, Frenquel.	Respiratory center in medulla.
Bradypnea	Chlorpromazine, Reserpine	Respiratory center in medulla.
Lachrimation	Mescaline, Histamine	Mammillary body to nucleus of VIII nerve. Area 8 of cerebral cortex through stimulation of anterior hypothalamus.

TABLE II

Special Effects After Intracerebral Drug Injection

Pharmacological Effect	Effective Drugs	Possible Central Sites of Action
Abnormal Electrocardiogram	Chlorpromazine, Strophanthin derivatives.	Anterior and posterior hypothalamus.
Stage III, Plane II General Anesthesia	Procainamide, Quinidine, Adrenaline, Nor-adrenaline	Ascending reticular system, hypothalamus.
Analgesia	Chlorpromazine	Hypothalamus and brain stem.
Tranquilization	Chlorpromazine, Reserpine, Frenquel	Hypothalamus and brain stem.
Hypothermia	Chlorpromazine	Thermoregulator center.
Miosis	Reserpine	Optic chiasma, optic tract, pretectal region.
Ataxia	LSD, Mescaline, Chlorpromazine ATP, Hexamethonium, Frenquel, Ergonovine.	Motor area IV of cortex, Vermis of cerebellum.
Behavior changes	LSD, Mescaline, Ergonovine	?
Catatonia and Depression	LSD, Acetylcholine, Eserine, DFP, Bulbocapnine, Mescaline Chlorpromazine, Reserpine, Morphine.	Region of periventricular gray matter, area immediately above mammillary bodies and rostral to red nuclei.
Sweating	LSD	Centers in hypothalamus. Pre-motor cortex. IV ventricle and a center in the medulla.
Sham Rage	LSD, Morphine, Bulbocapnine	Posterior hypothalamus bordering tegmentum III ventricle lining caudad to entry of aqueduct.

(continued)

TABLE II (continued)

Scratching	Mescaline, 5-HT, Morphine, Eserine, DFP.	Distal wall of IV ventricle Anterior intraventricular portion of fornix nuclei of septum pellucidum to anterior commissure above and behind mammillary bodies.
Convulsions	5-HT, DFP, Acetylcholine, Curare Bulbocapnine, Eserine, Reserpic Acid.	Centrencephalic system of higher brain stem.

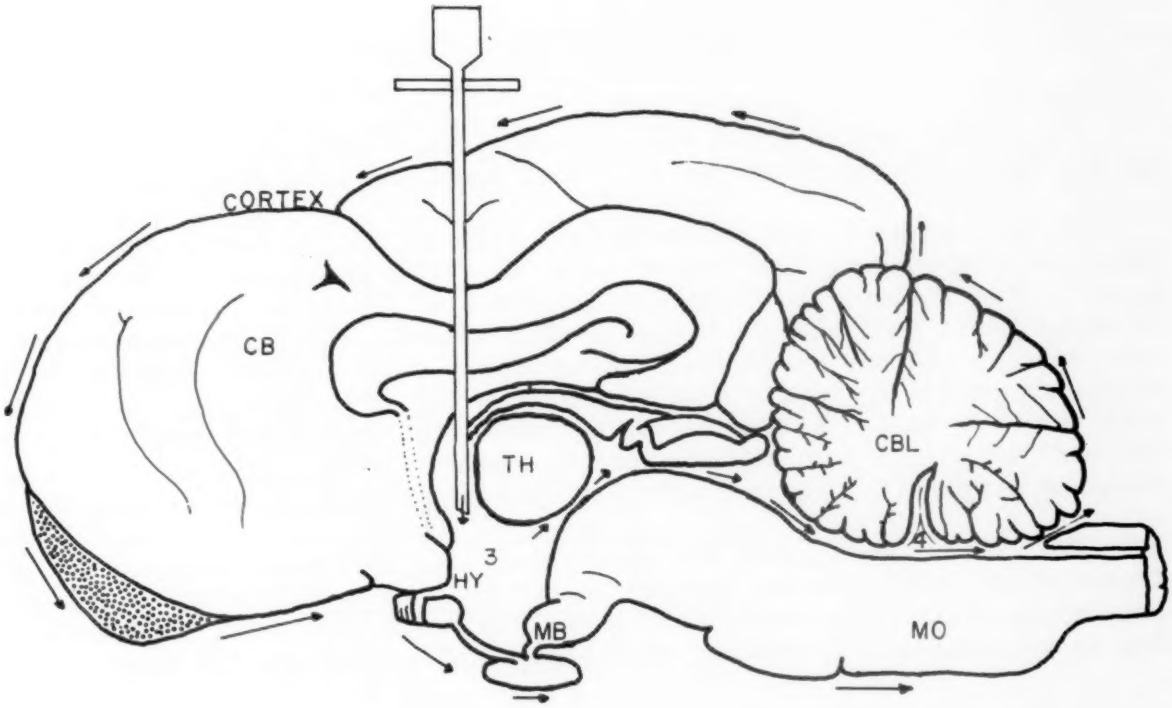

Figure 1: Median sagittal view of dog brain showing indwelling cannula. Arrows indicate circulation of cerebrospinal fluid; cerebrum, CB; cerebellum, CBL; thalamus, TH; hypothalamus, HY; third ventricle, 3; fourth ventricle, 4; mammillary body; MB; medulla, MO. (Courtesy, Haley, T. J., Journal of the American Pharmaceutical Association, Scientific Edition, 45, 605 (1956).

CLINICAL PROBLEMS WITH THE TRANQUILIZING DRUGS

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This paper is concerned with the problems in evaluating the effectiveness of the tranquilizing drugs and a discussion of the complications in their use.

It is estimated that approximately fifteen million Americans last year found it necessary to find relief from the stresses of life in tranquilizing drugs. Some estimation of the extensiveness of their use in varied branches of medicine is indicated in Table I. The amounts of 400 mg. meprobamate tablets used on the various wards of King County Hospital were computed for a six-month period in 1956. King County Hospital in Seattle is a general hospital with over 400 beds. Each ward has between thirty and forty beds. Meprobamate was used extensively on all the general medical wards. Because of its muscle relaxant properties, large quantities were prescribed on the orthopedic service.

The initial enthusiasm for these drugs has been somewhat dampened by the frequency of complications in their use. Dr. Winkleman, an authority on chlorpromazine, first suggested the drug could be used by general practitioners. (1) Now he recommends consultation with a psychiatrist before the drug is given.

Table II lists the complications seen in the use of chlorpromazine. There are only a handful of published reports on the undesirable reactions noted in the use of the other and newer phenothiazine derivative tranquilizers.

Reports by Rudy and associates (3) and Lesse (4) indicate that adverse side effects with promazine are milder and relatively uncommon as compared with those produced by chlorpromazine. However, a higher dosage is required with promazine. The similarity in chemical structure between the new tranquilizers of the phenothiazine derivative type and chlorpromazine would suggest that the same complications should be anticipated in using these drugs.

The minor complications (5) which in general reflect changes in autonomic function, include nasal congestion, dryness of the mouth, dizziness, and hypotension. They occur mainly in the first two weeks of treatment. They are not indications for stopping the drug nor ordinarily reducing the dosage. In their agitated state patients may become frightened by these complications and stop taking the medication. One young patient suffering from an acute schizophrenic illness following birth of her baby was prescribed promazine 50 mg. every four hours. As instructed she went to bed after taking the first tablet. After the prescribed half hour she arose quickly from the bed and promptly fainted. In falling she suffered a superficial laceration to her forehead. The paranoid aspect of her psychosis was stimulated by this and she stopped both the promazine and psychotherapy. The hypotension brought on by these drugs has resulted in a number of other secondary complications. I have known of several elderly

TABLE I

INPATIENT USAGE OF MEPROBAMATE TABLETS, 400 MG.

Service	Total/6 Months
2 North (General Medicine)	630
3 North (General Medicine	1,171
4 South (Infectious Diseases)	878
4 Center (Respiratory Center)	1,150
4 North (Neurology and Neruosurgery)	1,389
5th Floor (Psychiatry)	1,272
6 South (Orthopedics)	1,739
6 Center (Orthopedics, Urology)	2,038
6 North (Gynecology)	450
8 Center (Nursery)	50
8 North (Obstetrics)	50
9 Center (Surgery)	100
9 North (Surgery)	1,080
10th Floor (Pediatrics)	70
Total	11,967

TABLE II

COMPLICATIONS WITH CHLORPROMAZINE

Drowsiness	Photosensitivity
Dry mouth	Parkinsonism symptoms
Bitter taste	Jaundice
Hypotension	Convulsions
Weight gain	Deleria
Increased dreaming	Fever
Constipation	Agranulocytosis
Dermatitis	

The complications are listed in their approximate order of decreasing frequency. (2)

people on chlorpromazine or promazine who have suffered hip fractures from fainting early in the course of their treatment. One sixty-year-old woman at King County Hospital fainted and developed a cerebral vascular accident after the first parenteral administration of promazine.

Usually the major complications occur in the third and fourth week of treatment. They include the appearance of Parkinsonian-like symptoms, jaundice, various so-called allergic reactions, (6) and agranulocytosis. At least nineteen fatal cases of agranulocytosis in patients treated with thorazine have been reported.(7)

The Parkinsonian symptoms, unlike the other complications in this group, are related to the dosage used. These symptoms, notably tremor, are frequent but usually effectively managed by decreasing the dosage or adding one of the drugs used in the treatment of Parkinson's disease. Jaundice is seen in about 1 per cent of patients treated with thorazine. The drugs should be stopped in the event of jaundice. The jaundice is of the obstructive type and lasts usually two or three weeks. (8)

Table III lists the complications seen with Rauwolfia drugs. Symptoms indicating overactivity of the parasympathetic side of the autonomic nervous system include diarrhea, bradycardia, and gastrointestinal bleeding. In one series of 130 patients treated with reserpine over 10 per cent became depressed.(9) Both psychotic depression necessitating hospitalization and electric shock treatment and the less dramatic neurotic depressions have been described. This depression has occurred in patients treated with the Rauwolfia drugs for hypertension as well as those treated for psychiatric disorders.

Drowsiness often appears soon after meprobamate administration and usually lasts several days. As with the other tranquilizing drugs it is the most common complaint of patients on tranquilizers. Urticaria is the most frequent complaint of the remaining four symptoms in Table IV.

The uncommon occurrence of undesirable reactions with meprobamate in comparison with the Rauwolfia and phenothiazine derivatives has led to its wider use with nonhospitalized and the nonpsychotic patients.

There have been a number of reports of habituation to tranquilizing drugs, and several clinicians have described convulsions appearing after withdrawal from meprobamate.

It is perhaps too early to evaluate the effectiveness of the tranquilizing drugs when reports in the psychiatric literature vary from uncritical adulation to remarks by others that the tranquilizing drugs are no more than chemical strait jackets. (10) Some psychiatrists have shown partisan enthusiasm for an exclusively physical or exclusively psychotherapeutic approach to mental illness. Both the indications for and the value of these drugs are subjects of much debate. Stressing the negative side is the prophecy of two Portland psychiatrists (11) that continued increase in the use of these drugs could lead to the doom of our civilization. They say that tranquilizers take away even the normal amount of anxiety essential in our competitive society. These drugs, they intoned, could lead to a nation of tranquilized but torpid zombies incapable of productive or creative effort.

Others, happily their number is decreasing, hail these agents as new specific treatments and cures for our major mental illnesses.

What is the truth of the matter? Has a colossal hoax been perpetrated on the public and the medical profession by drug company hucksters? Or do these drugs truly bring tranquility to troubled spirits and deranged minds? Webster's Dictionary defines the word "tranquil" as "free of agitation or disturbance; calm, serene, placid, quiet, peaceful." Confronted with very disturbed psychotic patients who are violent or hyperactive the psychiatrist will find these drugs useful. We are much less confident that these drugs can free people of disturbed feelings or delusional thinking. It is doubtful if the drugs in themselves can make patients "serene, calm or peaceful." One wonders then if the term "tranquilizing drugs" is not a misnomer.

There is no question but that our large mental hospitals have been transformed in a way which is difficult to imagine. Some estimation of this change is evident in the figures recently released by Dr. Casey, Director of Psychiatry in the Veterans Administration. Introduction of new drugs has greatly decreased the use of the older somatic treatment methods. Electric shock treatment was used in 4,527 patients in the fiscal year of 1955, but only in approximately 1,000 patients for the first six months of the fiscal 1957. Insulin coma treatment was reduced from 1,486 patients in fiscal 1956 to only 383 patients for the first six months of fiscal 1957. One of the most dramatic changes was in the greater number of patients who could be given "privileges." This means that many more patients could be transferred from closed or locked wards to open wards and given the freedom of the hospital grounds.

Six years ago while working in a state mental hospital I frequently had occasion to visit the disturbed ward. One did not require directions then to find the ward, one merely had to follow the clamor and noise. One-third of the patients were in restraints with their arms tied to waist belts and the belts in turn attached to a chair. Many remained for weeks or months in seclusion rooms. On this ward electric shock treatment was given every day most often for the purpose of punishing or restraining the violent.

Recently when I again visited this same ward I was amazed by the quiet which prevailed. Patients were free of restraints and only one or two were in seclusion. Over half of them were on tranquilizing drugs. For the first time many were able to enter into relationships with other patients and with staff members. There are thousands of similar patients in our state mental hospitals who could benefit now from psychotherapy. Unfortunately it is seldom available.

Nearly all reports stemming from our mental hospitals agree that the phenothiazine derivatives and the Rauwolfia alkaloid and derivatives of Rauwolfia are most useful in patients who show severe anxiety and agitation. The apathetic, the quiet and the depressed are not helped and some believe these drugs are deleterious in these patients.

There is some evidence that the drugs in addition to making life more bearable for these patients have actually allowed some to leave the hospital who would, without these drugs, have to remain hospitalized. From his unpublished

TABLE III

COMPLICATIONS WITH RAUWOLFIA

Drowsiness	Depression
Nasal stuffiness	Diarrhea
Dizziness	Bradycardia
Parkinsonism	Gastrointestinal bleeding
Urticaria	Habituation
Dermatitis	Hypotension

TABLE IV

COMPLICATIONS WITH MEPROBAMATE

Drowsiness
Urticaria with or without fever, nausea and vomiting
Fever
Arthralgia
Purpura

studies of the effects of the tranquilizers in the mental hospitals in New York, Dr. Nathan Klein has stated that from 5 per cent to 7 per cent of the total hospital population who would otherwise not be discharged, will be able to leave the hospital.

In this context it is well to remember that most of our large mental hospitals provide mainly custodial care. A notable exception is the Topeka State Hospital which became a training center affiliated with the Menninger Foundation after the last World War. (12) The number of psychiatrists was increased from three to twenty-three and psychotherapy was made available to patients who had previously seldom seen their physician. The average daily census in the past ten years was reduced approximately 25 per cent. Where other state hospitals providing mainly custodial care are only able to discharge fewer than 50 per cent of newly admitted in the first year of hospitalization, it is able to discharge 82 per cent. This is a far better record of success than that obtained more recently by the drugs in other hospitals.

Most psychiatrists believe that in a few cases of very hyperactive and excited psychotic patients it is possible to avoid hospitalization by the combined use of tranquilizing drugs and psychotherapy. Also most concur that the length of hospitalization in many is reduced. Unfortunately these are only impressions not backed at this time by any controlled studies. Although of great assistance in managing the chronically disturbed psychotics, the drugs have not permitted very many to leave the hospital. One study, for example, reported only one remission out of 190 hospitalized chronic schizophrenics treated with chlorpromazine over many months.(13)

The task of evaluating the beneficial effects is difficult. What portion of the benefits derived with psychotics shall we ascribe to: 1) the suggestion or placebo effect; 2) the pharmacological action; 3) other secondary therapeutic influences brought about by making patients amenable to other forms of therapy?

Careful studies by Beecher and others have shown that approximately 35 per cent of general patients react to a placebo with improvement in a manner indistinguishable from an active pharmacological agent. (14) People working in our large mental hospitals have long known that each time a new treatment is introduced nurses, attendants and doctors would for a time communicate their interest and enthusiasm to their patients who would in turn improve. Trudeau's advice to his medical students in the last century was "Make haste to use the new drugs while they are still effective." One psychiatrist studied the results of different psychiatrists using the same tranquilizers with comparable patients. The patients of some of these physicians benefited markedly; those of others little or not at all. These differences were highly correlated with the attitude of the physician. Patients whose physicians were enthusiastic improved. Doctors who were skeptical had poor results with the tranquilizers.

As yet we cannot describe the pharmacologic action in terms of the mode or site of action. Many believe that the immediate pharmacological action is not so important as the benefits gained from making patients accessible to other therapeutic agents. Free of restraints and seclusion, patients are now able to establish meaningful relationships with other people. As patients have become less

violent and disturbed, attendants are less fearful and hostile to them. Individual and group psychotherapy, occupational therapy, recreation, work and just the capacity to talk and be with people are open to them now.

The most laudatory accounts of the tranquilizing agents have come from the large state hospitals where the staff-patient ratios are lowest. In the few mental hospitals where there are adequate numbers of staff to use psychotherapeutic methods, fewer drugs are used.

Pinel Sanatorium in Seattle, a small private psychiatric hospital with an unusually high number of staff to patients, has not used a single tranquilizing agent in the past few months. There, when a patient becomes very agitated or violent, physicians and nurses may spend hours with him helping him through the turmoil. This, of course is impossible in our state hospitals with their serious shortages of personnel. As one psychiatrist at Pinel said, "We can do a better job using people than the doctors in the state hospitals can using tranquilizing drugs." Psychotherapy can take the place of tranquilizing drugs, but tranquilizing drugs cannot substitute for psychotherapy.

Shifting our attention to the use of tranquilizing drugs on patients treated in the office we find reports much less encouraging. It is a fact that no one has yet proven that the ordinary psychoneurotic shows any greater benefit with tranquilizing drugs than with a blank placebo. (15,16) For chronic neurotic patients the drugs can only afford temporary and illusory benefits and certainly no change in the underlying psychological causes of their disorder. Probably the greatest value of these drugs in office or outpatient treatment will be in the relief of acute and severe panic and anxiety. Recently I treated a 58-year-old woman with symptoms of severe anxiety, insomnia and headache of muscle tension origin following the death of her husband. For years she had suffered from an obsessional neurosis. Overwhelmed with fear and loneliness she was unable to make the burial arrangements. Prescription of meprobamate 400 mg., t.i.d. and two tablets at bedtime gave her sufficient relief to sleep again and manage the affairs connected with her husband's death. Three weeks later the drugs were stopped and she continued to work in psychotherapy on her emotional problems.

If the tranquilizers have no lasting effect upon the course of the simple psychoneuroses, how are we to assess their popularity? Using some of the same advertising techniques which Madison Avenue uses in selling soap, the drug companies have taken over the postgraduate psychiatric education of many physicians. A casual inspection of several recent general medical journals shows as much as 30 per cent of the advertising space taken up by tranquilizing agents.

All of us, doctors and patients alike, still retain some of our infantile belief in magic and may hold to the irrational hope that a pill will somehow remove our deepest troubles. Many doctors who formerly lacked either the inclination or the time to treat their neurotic patients now look to these agents as a new panacea for all kinds of emotional ills. Unfortunately our culture accepts physical illness more than mental illness. Patients would rather receive a drug than think that their difficulties arise from within themselves and their disturbed relationships with others.

Summary

The undesirable reactions experienced in the use of chlorpromazine, the Rauwolfia drugs and meprobamate have been discussed.

Chlorpromazine and the Rauwolfia drugs have been of proven value as adjuncts in treatment of the psychoses in which there is excitement and excessive psychomotor activity. Much of their value is probably attributable to making patients available to other therapeutic influences in their environment. In the few mental hospitals which have adequate treatment facilities their use has been limited to mainly emergency and short-term use. Hospitalization has been prevented in many patients with acute psychoses through the use of the tranquilizing drugs in combination with psychotherapy.

Meprobamate has been most effective in acute, nonpsychotic disturbances characterized by moderate to severe anxiety. It has the ability to reduce skeletal muscle tension.

Perhaps the most serious complication in all of the tranquilizers has been the tendency of many patients with the tacit consent of their physicians to substitute the drugs for psychotherapy.

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Friday Session

GRADUATE TRAINING AND RESEARCH IN PHARMACOLOGY

George L. Webster

Chairman

INTRODUCTION

George L. Webster

University of Illinois

The topic for today is Graduate Training and Research in Pharmacology. Since this is a discussion initiated by and on behalf of the American Association of Colleges of Pharmacy, it is implied in the title that the graduate training and research referred to is that to be given and conducted by the faculties of the colleges of pharmacy which are equipped for it.

The task facing faculties of these colleges is really two-fold; first, they must arrange to prepare graduates who are not only the equal but actually the superior of those coming out of the departments of pharmacology in medical schools, and second, they must somehow convince college and university administrators and industry employers that their graduate programs are the equal of those in the medical schools. Perhaps equally important, they must convince their graduates of the excellence of their programs. These two objectives have two psychological hazards to overcome. The teaching of pharmacology as a part of the undergraduate curriculum in pharmacy is relatively new, and graduate teaching in these colleges is even less old in years. Hence, there are some who look at the situation in somewhat the same spirit that people look at a high-school horse performing a dance. They are moved to applause not because the horse waltzes well, but because he can create the illusion of waltzing at all. Such an uncritical attitude, I submit, does more harm than good. The other attitude is one of automatic rejection of the whole idea that pharmacology, a discipline traditionally closely associated with the medical curriculum, could be adequately taught outside of those sacred confines.

On Monday Dr. Green suggested that the undergraduate instruction in pharmacology should be such as to develop a professional rather than a scientific attitude toward the subject. If this is adopted as the objective it may be difficult to interest the right type of student to go into the graduate study of pharmacology or if interest can be developed, the proper prerequisites will be missing, thus delaying the development of graduate discipline.

Other speakers have pointed out examples of the type of knowledge which an undergraduate should have and some of the areas which need investigation in order to develop pharmacology as a science basic to the knowledge of drugs and therapy. What needs to be emphasized, it seems to me, in graduate training programs and in pharmacologic research is the basic science aspect of both. Pharmacology utilizes the tools of physical science to achieve useful knowledge of the functioning of biological entities under normal conditions and when challenged by drugs. It is no longer advanced by the technique of observing the effects of injecting a natural or synthetic chemical into the largest number of animals obtainable. Instead, the pharmacologist must know and use the sciences of mathematics, chemistry, and physics so that his experiments may have meaning. It is no longer proper, if it ever was, to confine the graduate training to the department of pharmacology, no matter how distinguished its faculty may be. The quality of other departments in the graduate school is equally important.

OBJECTIVES OF GRADUATE TRAINING IN PHARMACOLOGY

Victor A. Drill*

The discussion of the objectives of graduate training in pharmacology is a broad topic and obviously open to many different approaches. This morning I will limit the presentation on the training of graduate students to those seeking the Ph.D, degree in the college of pharmacy or the school of medicine. We can further eliminate special fields such as veterinary pharmacology or insect pharmacology from the detailed part of the discussion. In the field of medical pharmacology, with which we are chiefly concerned, we can divide our objectives into three areas. I would like to mention each objective briefly and then discuss some aspects of the objects and methods of achieving those goals. We may not all agree on the broad objectives and I am sure we will have some differences of opinion on the details. Nevertheless, the presentation may be of some value if it serves to stimulate discussion of this very important aspect of pharmacology.

Three Objectives

Objective I. Didactic Studies: Didactic course work should provide the nucleus of the graduate program. Such studies may be approached from various viewpoints and perhaps we can consider this area by dividing our program into three broad areas: (a) basic courses that are necessary and preliminary to a pharmacology course, (b) related courses that are necessary for a better understanding of pharmacology and its important interrelationship, and (c) pharmacology courses, both introductory and advanced in nature.

Objective II. Correlation and Stimulation: Our second objective should be to stimulate the intellect of the graduate student. Here our over-all aim is to bring out as much as is possible the originality that is within the student and to aid him in developing clarity of thought. Such efforts will of course depend to a large degree on the caliber of the graduate student, but whatever stimulation we give during his graduate training can only benefit his ultimate efforts as a teacher or investigator.

Correlation is an important part of this training and the graduate student should correlate his knowledge of drug actions with what he has learned in the other basic disciplines and in related courses. He should be able to evaluate literature in terms of correlation so that when he reads of a new analgesic drug he can evaluate the information in the paper and correlate it with his knowledge of pharmacology, physiology, and biochemistry so as to have a rounded picture of the drug in question and its worth in comparison with other drugs. We want him to be able to evaluate new drugs so that he may be able to find agents which

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offer therapeutic advantages over substances now available. He should be original, also, in the sense that as he comes across an odd reaction of a new drug he may be able to correlate this odd reaction with some other disease picture or disease state so as to direct the development of this drug in a totally different direction from what he had earlier supposed.

Objective III. Experience: The third of our objectives is to give the graduate student experience. This is accomplished by undertaking research problems and assisting in the teaching program. The discipline of research is usually encountered in working for the master's degree and the initial problem may be relatively simple. As the student works further, towards his doctorate, he may enlarge on the same problem or begin an entirely new project. Although important, such investigative work is necessarily limited. However, the problem should be sufficient in scope so as to demonstrate the scientific method and the philosophy of research and to stimulate the student to further investigative work.

Experience can further be offered during the last one or two years of graduate study by having the candidate assist in laboratory teaching. This should be a required experience. In such work he is faced with the problem of helping students interpret their data, discussing problems with them, asking about the drugs used in the laboratory exercise, and discussing the results obtained and the relationship of the drugs to normal physiology and biochemistry. This experience can be very valuable, and such a performance will make the graduate student read, study, and think. Selected students should also give one or two lectures during their last year of study. The graduate student should know how to organize data, not only from the standpoint of doing research and presenting reports, but also from the standpoint of being a good teacher--to organize in the sense that he can develop a topic and present it well at a lecture or at a laboratory session.

Achieving the Objectives

In presenting certain objectives as the goal of a graduate program in pharmacology, I have had in mind a number of points which it may be well to bring out at this time, because, if we agree on them, we can more readily plan a concrete program. I would say, for instance, that a pharmacologist has to call on more skills than does any other biological or medical scientist. As drugs overlap into so many different fields ranging, for example, from anesthesiology to the treatment of various infections, psychoses, or dermatological problems, the pharmacologist has to have a fairly broad background of knowledge in order to have some information in each of these fields. Secondly, in planning our program we must realize also that the pharmacologist measures drug effects. In fact, I think we can say that it is impossible to develop new drugs either for animals or for man without the services of the pharmacologist. The physiologist cannot develop new drugs nor can the biochemist or the clinician. It is up to the pharmacologist to make his evaluation of new drugs from the standpoint of understanding the animal correlations with a disease picture, to determine safety from various fundamental aspects, and to evaluate toxicity in subacute and chronic toxicity studies. In teaching, particularly in medical teaching, pharmacology serves to correlate the basic courses with the clinical courses and the pharmacologist has to have broad training to bring this relationship to the student.

Basic Courses: With these points as background, we might discuss a little more the actual courses to be offered to the graduate student in medical school or the graduate school in a college of pharmacy. In a sense what we will outline is practical, although partly idealistic, as presentations at different schools will vary considerably. As basic courses we should require that the graduate student have thorough training in physiology, in biochemistry, and, with some modifications, in anatomy. Certainly the student has to know the normal functionings of the body quite well in order to learn pharmacology. Biochemistry is involved in so many ways I don't think we would have any question of including it as a basic course. Anatomy should be offered in a modified form as the graduate student does not need the detailed anatomy of the arm, leg, hand, and other organs. I believe that the anatomy of the chest and of the abdomen, since the organs there will be concerned with drugs, should be discussed in detail. He should know the anatomy of such areas fairly well. He should also know the central nervous system, spinal cord, autonomic nervous system, blood vessels, etc., but not all the details of bone structure or the origin and innervation of all the muscles. Most of such detail, often given to the graduate student in the medical school, is a waste of time.

Related Courses: Working from these three basic courses we can then outline a secondary group of didactic courses which might be called related course work. This is an area that will vary considerably among different schools. Microbiology might be considered under such a heading. To really understand antibiotic drugs the student needs to have some idea of why we want alterations in absorption, blood levels, maintenance of blood levels, and diffusion into certain areas. He should know the different groups of organisms, their classification, and something of the disease picture so that he can better understand the application of antibiotics to the treatment of infections. Histology might be listed as a related course, as well as pathology--not necessarily the detailed pathology that is given in the medical school, but certainly a course in pathology, because so many of our drugs do produce pathologic effects. If courses are available in neurophysiology and neuroanatomy they should also be included. Such are particularly important for we are now developing a whole new area of psychopharmacology, as discussed earlier in this seminar.

We can modify the related courses, and this is done in other schools, to stress more the chemical aspects of pharmacology. Pharmaceutical chemistry, extra courses in organic chemistry, and physical chemistry may be substituted in part for biological courses. In other words, we are faced with the problem that the field of pharmacology is now so large that one cannot hope to cover everything, so that of necessity our related course work will vary among schools and we will develop graduate students with different emphases in their graduate training. Some will be oriented more toward chemistry, biochemistry, or pathology, and still others, perhaps, towards microbiology. No one school can cover all of the related course work in attempts to develop pharmacologists who would be familiar with all aspects of pharmacology. Such development is practically impossible.

Pharmacology Courses: Following the basic courses, and in conjunction with or following related courses, the student is ready to begin work in pharmacology. He will certainly need the basic courses as background to pharmacology and, as he is beginning to major in this area, some related course work. The student should

then take the basic course in general pharmacology being offered by the school, but his training in pharmacology should not stop at that point! Certainly the person who goes through medical school and receives an M.D. degree has had a course in pharmacology, but such a person is not a pharmacologist any more than he is a physiologist or a biochemist because he has had a course in that subject. One should offer advanced courses in pharmacology, such as I understand is being done here at the University of Washington. These courses will involve the presentation and evaluation of basic mechanisms in various areas, as, for example, you heard described in the session on cardiovascular pharmacology. Other courses may also be offered, such as the pharmacology of anesthetic drugs. There may also be joint courses between departments to explore the effects of drugs on enzyme systems--a course for graduate students both in biochemistry and in pharmacology. A topic such as drug metabolism should be offered if at all feasible. Toxicology is still another subject. A course in methods should also be given whenever possible. Methods are not important as such because a capable person can read a method and apply it. For the graduate student, however, such a course does give some idea of techniques in various fields. In actually carrying out some of these methods and trying to interpret results the student is again forced to think, and to explain results which are expected, or which do not fit the usual patterns. Statistics or experimental design has to be covered and pharmaceutical chemistry should be offered.

The graduate program in pharmacology becomes quite large when we consider all of the courses in pharmacology and the related courses that might be offered. Obviously we are not going to be able to cover everything and the emphasis on different subjects will vary among the schools and will also be determined in part by the specialization of the student who may become more interested in chemistry, toxicity, drug metabolism, or the pathologic correlations of pharmacology. I think, then, following also what Dr. Webster said, that there is a need for both the pharmacy school and the medical school in training graduate students in pharmacology, as the schools will differ in their emphasis, particularly in the curriculum. In each area we should strive to offer good courses as basic subjects, as related courses, and as special topics for the major in pharmacology. Stimulation of the intellect of the student, as we are attempting to bring out his ability to evaluate, to correlate and to integrate, can be done by journal clubs, literature surveys, and seminars, wherein the student presents reports on a given subject. Joint seminars between departments should be attended. In seminars, for instance, I would not have the graduate student report only on the progress of his research. I would like to see the graduate student be assigned a topic unrelated to what he is doing for his research problem. For instance, one might give as a topic the subject "pharmacology and therapeutic uses of propylthiouracil." This would serve to have the student read papers which he might not ordinarily look up, and to evaluate them and present a report to a student-faculty seminar. I would limit the topic so that it would not take too much of his time and limit his presentation to 20 or 30 minutes, but I would pick odd topics of that type, limited in nature, outside of his general research group. Usually university lectures are available as part of a broad educational program, and the student should attend lectures, not only of general scientific interest, but also subjects outside the realm of general science.

The Graduate Student: Well, perhaps, we don't agree on points mentioned so far. If, however, we do agree on them, we then have to try and carry them out, and this is not simple. First of all in the graduate program we have to have not only students, but a good caliber of students. One speaker, on the first day of the seminar, mentioned selling ourselves in pharmacology. I think I would apply this thought from another aspect--selling the field to students--so that they will become interested and want to do work in pharmacology. In the colleges it is rare for a student to hear the word pharmacology or to know of pharmacology. The average college student knows of physiology, biochemistry, comparative anatomy, and organic chemistry because those courses are offered in the undergraduate college curriculum. It is only when a student goes to medical school or pharmacy school that he hears of pharmacology. The student in medical school is most likely to go on and practice medicine rather than ever become a pharmacologist. The student in the college of pharmacy, however, being exposed to the undergraduate work may go on to graduate work, and perhaps it is with these students that we can do a better selling job and get such individuals interested in pharmacology as a career. Between the colleges of pharmacy and the medical schools, as I mentioned Monday, we presently graduate a total of fifty to sixty Ph.D.'s per year--a very small number.

The Graduate School: Graduate work in pharmacology can be undertaken in either a college of pharmacy or a college of medicine, the prime requisites being a satisfactory program and an adequate faculty. The medical schools have, for various reasons, tended to overshadow the pharmacy schools in such graduate training, although good and poor graduate programs can be found in either area. Each school has something to offer, and the well-trained man in either area can be an asset to pharmacology. However, I do think that the colleges of pharmacy which offer graduate programs have to strengthen the basic course work given preliminary to pharmacology, and strengthen it at the graduate level. This is particularly true of physiology and biochemistry. I am well aware that these courses may be adequate in certain schools, but, in general, I believe improvement is needed. Since we have some deans attending the seminar, it might not be amiss to point out that carrying out this objective places a good deal of responsibility in such an office to provide both adequate faculty and facilities for pharmacology. Very often pharmacology tends to be neglected in one or both areas. To carry out such a broad program in graduate training in pharmacology and to have good basic courses in physiology and biochemistry is not only of value to the graduate student in pharmacology, but also to the whole undergraduate body.

The problem of broadness or lack of broadness in many teaching programs has bothered me a good deal. If one looks at some departments in schools throughout the country, he finds a great deal of specialization within the department. Certain departments, whether in physiology, biochemistry, or pharmacology, may be organized more or less in a team all working on one problem or project. This all too frequently produces an unbalanced teaching program that can only be to the detriment of the undergraduate or graduate student. The reason for having the staffs we do at the colleges of pharmacy and at the medical schools is primarily for teaching. To carry out this responsibility, the teaching staff should be one equipped to cover the various aspects of the subject. Research is important and necessary, but should not operate to the detriment of a good teaching program.

Lastly, in carrying out these objectives a good deal of responsibility falls on the faculty member who takes a person as a graduate student and attempts to guide him through such a program to his degree work. There should be some support for the graduate student, and the faculty member should be aware of what fellowships are obtainable. It is important that the faculty member not take too many graduate students. I don't know where one would draw the line, but I think it is obvious that one man cannot handle 12 graduate students. He might, on the other hand, be able to handle one, two, or three students. The faculty member should help the student to obtain his first position. He should recommend, so far as he understands the student, the next step in his career. Should a person finishing graduate work be recommended to a department that does excellent research work but perhaps poor teaching, or would one prefer to send this student to a department noted for its good teaching? What further training does the student need at the time he finishes his graduate studies?

Summary

Pharmacology is a very large area and aside from general concepts and knowledge of commonly used drugs no one person can hope to know but a limited part of this field. Nevertheless, I believe we do have to offer the course work and the stimulation necessary to give the student as broad a training as possible--at least to form the basis for the common concepts and general knowledge within pharmacology. When the graduate student receives his degree he is only beginning and, as ourselves, must study pharmacology the rest of his life in order to keep up with the advances that are constantly occurring. This is, of course, the reason for the present seminars and our attendance and discussion together.

COURSE REQUIREMENTS FOR THE PHARMACOLOGY GRADUATE STUDENT

E. Leong Way

University of California

Four years ago I had the privilege of speaking before the Section of Teachers of Biological Sciences of the American Association of Colleges of Pharmacy on a topic in a similar vein to the one I am speaking on today.* The passing of time has served to fortify my views and perhaps it will be timely to project and expand these opinions again before this group. I shall not ask the indulgence of those who have heard or read about these views but only of the few who may have remembered something of what I have expounded.

The first speaker this morning has indicated that, in order to develop responsible citizens whose contributions to society will stem largely from their specialized interests and aptitude in pharmacology the objectives must be comprehensive to cover a wide range of activities in a broad scientific discipline. The graduate program in pharmacology, therefore, should be oriented towards producing more than just a trained individual capable of performing the specific functions and occupations of the profession. Even more important, it should be directed toward developing creative and intellectual leaders of the highest integrity and character in pharmacology.

A sound program for graduate study in pharmacology recognizes that pharmacology is a broad scientific discipline whose frontiers cannot be sharply defined from its parent and sister disciplines of physiology, biochemistry, toxicology, microbiology, and psychology, and that advances in pharmacology stem from advances in these fields. Qualified students with diversified undergraduate backgrounds in the various physical and biologic sciences, therefore, have much to contribute towards the advancement of pharmacology. We have found from personal experience in our laboratory that the mathematician, physicist, chemist, biologist, pharmacist, dentist, veterinarian, as well as the physician bring with them novel and refreshing ideas and technics to solve pharmacologic problems. Consequently, the general course requirements should be flexible in order not to discourage students in fields other than medicine and pharmacy from entering graduate studies in pharmacology. This is of particular importance because I know of no school which offers a major in pharmacology to the undergraduate. If one exists, it is a rarity. In fact, with the exception of students matriculating in the health sciences, students in other basic disciplines seldom get the opportunity to become even cognizant of the term pharmacology, although I recognize that there are institutions that make such courses available to the undergraduate on an elective basis.

At the University of California, the wide scope and diversity of pharmacology is acknowledged by offering the graduate degree in Comparative Pharmacology and Toxicology on a general university basis. The requirements are administered by a

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* Am. J. Pharm., Ed. <u>18</u>, 31-37 (1954).

group of the faculty representing various departments of the university interested in comparative pharmacology. Such a program recognizes that the application of pharmacology extends beyond the clinical branches of medicine into veterinary medicine, dentistry, pharmacy, public health, agriculture, sanitation engineering, criminology, forensic toxicology, industrial toxicology, and other fields. While the Department of Pharmacology of the School of Medicine still plays the pivotal role in the traditional training of professional pharmacologists, a graduate student instead of being restricted to working in the Department of Pharmacology can, if he desires, elect to work with selected staff members of other departments. Among this group currently are representatives from physiology, biochemistry, pharmaceutical chemistry, veterinary medicine, dentistry, anatomy, pathology, biophysics, medical physics, radiology, microbiology, parasitology, and entomology.

Adequate preparation in comparative pharmacology and toxicology requires a well-balanced background in the physical and biologic disciplines. The program is made flexible, particularly for students with a background in physical sciences, by allowing for completion of certain deficiencies during the course of graduate study. Bachelor's degrees in chemistry, physics, pharmacy, or any of the biologic sciences, as well as professional degrees in medicine, dentistry, pharmacy, or veterinary medicine are considered to provide suitable background for graduate study in pharmacology. The specific undergraduate prerequisite for pharmacology has been adequately outlined earlier by Dr. Daniels and concurs well with my own views. I wish only to echo for emphasis that pathology is an important prerequisite to pharmacology in addition to the background usually recommended in physiology, biochemistry, and anatomy. The mechanism of action of diuretic drugs and their application and limitations can only be fully understood when one has a basic comprehension of the pathologic physiology of edema formation as well as the physiology and biochemistry of the kidney.

Prerequisite courses to pharmacology offered in the professional schools, however, do not always meet the need of the graduate student in pharmacology. He is often required to take intensive survey courses in anatomy, pathology, and microbiology with professional students because some training in these disciplines is necessary and the courses happen to be the only ones offered. There is need for less intensive prerequisite courses to pharmacology which still retain the meat and the flavor of the disciplines. Such courses should give less emphasis to the factual knowledge in the field but still project the philosophy and methodology of the discipline. Although the student may be less familiar with details, he would have a better comprehension of the subject matter covered and quite possibly of the discipline itself. I strongly feel that although massive presentation of descriptive material may equip the student from the practical standpoint for a year or two, great harm may be done by stultifying the student's ability to self-educate.

What constitutes a sufficient background in pharmacology is an extremely difficult question to answer. If one should pose the question today to a professional pharmacologist---"What is a well-trained pharmacologist?"--I would expect a variety of answers which would reflect at least, in part, the specialized interest of the individual polled. If one were to accept all the answers, it would be obvious that it would not be possible to equip the graduate student with all the knowledge and technics in a period of four years. There is probably more

augmentation of descriptive material in pharmacology than in any other basic discipline. Much factual matter which can be of practical importance for a short while is here today and gone tomorrow--as witness the fate or near fate of many antiseptics, the sulfones, arsenicals, sulfa drugs, chloroform to mention but a few. In the meantime, within the past ten years, completely new pharmacologic fields have been opened up by the introduction of antibiotics, antihistamines, tranquilizers, tuberculostatics, and agents for the treatment of cancer, while new techniques have given fresh insight and expanded our knowledge of the classical agents. Countercurrent, chromatographic and radioactive technics have yielded much information as to the metabolism of morphine and other narcotic analgetics. Stereotaxic and electrical recording procedures have revealed clues as to the sites and mechanisms of action of the barbiturates, the anesthetics, and other well-known centrally acting agents. As indicated at this seminar, many of the earlier concepts on the actions of digitalis on the cardiovascular system have been discarded and revised after its effects were studied in man by means of special technics for measuring cardiac size and output, circulatory velocity, venous pressure, peripheral resistance, and changes in conduction in cardiac muscle.

Newer concepts concerning serotonin and serotonin-releasing substances, histamine-releasing agents, P substance, neurohumoral activation of the anterior pituitary, and central inhibitory substances are certain to have vast pharmacologic implications. Indeed, advances and discoveries in our knowledge have been so numerous and widespread that even the specialist experiences difficulty in keeping abreast with the course of events. Thus, in pharmacology there is a greater challenge to the teacher than in any other field to stress principles and proper interpretation and significance of methods and results in order to cultivate in the student those basic understandings, attitudes, habits of mind, and mental skills to enter the profession. This calls for sound initial planning. Descriptive offering of factual material, no matter how new, will not serve as a stimulus for further learning nor prepare the student to meet a changing world.

I think that we would all agree that principles take precedence over factual material. We would probably have considerable disagreement, however, as to how much factual knowledge and laboratory training are necessary to give the student mastery in the field. Certainly there is no unanimity of opinion with respect to the latter matter in our own Department. The scope of pharmacology is such that it exceeds in breadth those of its parent and sister disciplines because pharmacology utilizes from many and finds wider applications in many other fields. Moreover, it may be studied from the molecular level to the sociologic level. As a consequence, any graduate program is a compromise which should reflect the assets of the institution. Each insitution should direct its effort in the development and improvement of a graduate program in pharmacology so as to make most effective use of its personnel and facilities. Such problems as to whether a student with strong interests in neurophysiology should be required to take intensive course work in microbiology and chemotherapy may best be dealt with individually, taking into consideration the ability, maturity of the student, and an analysis of his objectives.

Specialization is an inescapable consequence of research but ability to solve a research problem is dependent on broad training which places emphasis on

recognition and understanding of problems, organization of plans of attack, execution of the plans, and drawing sound conclusions. Consequently, advanced training in pharmacology should cover some instruction in as many basic fields as is practically possible, since in most instances the potential graduate has no way of determining in which specialty area he will operate upon completion of his training. There must be a common core of courses, however, which prepares the student to work within the area expected of a professional pharmacologist.

The principles of bioassay are of paramount importance. Bioassay represents quantitative pharmacology and in essence every pharmacologic experiment is a problem in bioassay. The statistical calculations and laboratory procedures in biological standardization and screening are only the operational means toward an end. Statistical analysis is an accepted and expected part of a pharmacologic experiment which provides a basis for the evaluation of raw data. However, I continually have to remind myself and my students, that the statistic is merely an elegant refinement to facilitate the drawing of a conclusion; the judgment is made by the investigator and not the figures. The finding of a statistically significant elevation of the tail response threshold to a noxious stimulus in a rat after administering a pharmacologic agent does not necessarily mean that the agent is an analgetic either in a patient or, for that matter, in the animal tested.

Advanced course work in physical chemistry, particularly in theoretical organic chemistry, is essential for a critical appreciation of pharmacology at the molecular level. Coverage of electronic structural theory (without necessarily digressing too much into quantum mechanics), atomic and molecular structure and their relationship to charge distribution, resonance, bond distance and angles are important in biochemorphic considerations as to the mechanism of actions of drugs. The recent rapid advances in our knowledge about choline esterase inhibitors could not have been made without an understanding of such factors. The graduate student who is not in position to appreciate these fundamental considerations is not adequately prepared.

We can develop the thesis further and maintain that a course in enzymology, with principal emphasis on structure, kinetics, and mechanism of action of enzymes, is equally necessary for an appreciation of pharmacology at the biochemical level. Course work in cellular physiology and biochemistry is important to carry the graduate to the next higher level where much in the future advancement of pharmacology is yet to be made. There appears to be no limit to the amount of training in comparative mammalian physiology which would not be of value to the pharmacologist. I need but to mention the newer developments in neurophysiology, endocrinology, and renal physiology which sparked, respectively, the introduction of tranquilizers, newer corticoids, and some novel types of diuretic agents. Finally, an exposure to applied pharmacology would often give a better understanding and a clearer perspective of the mechanism of action of many pharmacologic agents.

The requirements, as outlined above, are desirable but would be impractical insofar as the time element is concerned. Perhaps a solution can be effected by a single intensive graduate course in advanced pharmacology which incorporates all these disciplines and draws upon their doctrines and technics. The course should aim to integrate the information gathered at all levels and interpret the mechanism

of action of drugs on a vertical basis. It is this unique role of the pharmacologist which distinguishes him from a physiologist or a biochemist. Let me state at this time that such a proposal is not original, but that I am a strong advocate of this concept which is being seriously considered as a graduate requirement in our own Department.

The advanced course in pharmacology would be a sort of local symposium in miniature but it should show greater continuity of thought than the symposia presented on a national basis which often mirrors the specialized studies and interests of different individuals working in a common field. The topics could be rotated on a three- to four-year basis to enable graduate students at various levels of instruction to participate together in the course without the necessity of repeating subject matter during their training period. One instructor should be responsible for the course but it is of utmost importance that staff members of the same and different departments participate in the instruction. As an example, the pharmacology of morphine-type narcotic analgetics could be covered by inviting an interested anatomist or physiologist to discuss critically pain mechanisms before a consideration of analgetics and quantitative measurements of analgesia is begun. Physical and pharmaceutical chemists could be asked to participate in the physicochemical and biochemorphic aspects of analgetic compounds. Physiological chemists could be called in to contribute on the cellular and enzymatic aspects of morphine action. However, it should remain the task of the pharmacologist to integrate the knowledge about various drug effects at various sites and levels and relate in an organized manner the over-all effects of the drug. Such a program correctly implemented should enable qualified individuals to gain an advanced critical appreciation of the principles, facts and methods of pharmacology and develop their capacity for enlargement of such knowledge independently. They would in every sense be responsible citizens and scientists who would make useful pharmacologic contributions for the service of mankind.

SUPPLEMENTAL TRAINING AT THE GRADUATE LEVEL

Ewart A. Swinyard

University of Utah

The academic pharmacologist has two responsibilities--one to his subject or field of specialization and the other to his service as a teacher. As a specialist he is expected to make contributions in the form of original research, to be dedicated to his particular field of learning, and to believe in its value for mankind. As a teacher he is expected to inspire others to acquire useful skills, worthwhile ideas, sound attitudes, and intellectual powers. Therefore, a university or college professor is two things--a specialist and scholar, and a teacher.

How well is he trained to carry out these functions? Usually, the university pharmacologist is well trained in his subject; his academic degrees are accepted as evidence that he has acquired essential knowledge in this particular field and that he has the ability to do original research in this area of specialization. However, as a teacher he probably has had little or no special preparation. Indeed, as our graduate schools function today, the student rarely has either the time or the opportunity to familiarize himself with the fundamentals of good teaching. In order to overcome this deficiency, it becomes necessary to devise ways and means by which he can acquire these skills, either after he has assumed obligations as a teacher or before he has reached this stage in his academic development. The devices which may be employed are, at least in this presentation, defined as supplemental training.

The importance of supplemental training at either the graduate or the postgraduate level is indicated by the fact that seminars, such as the one which we have been participating in this week, were originally conceived with the idea of correcting, in some measure, recognized pedagogic deficiencies in our pharmaceutical faculties. "The primary purpose of these seminars," as stated in the report of the Pharmaceutical Survey, "is that of providing needed opportunity for the members of the teaching staff and for graduate students to come into fruitful contact and to keep pace with progressive content and methods of pharmaceutical teaching." Indeed, the 1954 seminar on pharmaceutical education was directed entirely toward the principles of learning and teaching. It seems paradoxical, therefore, that the faculties of colleges of pharmacy should enthusiastically endorse the subjects presented in these seminars and virtually ignore them in their own graduate programs. This lack of concern results from several circumstances. One is that in many colleges there is little recognition of good teaching. Often the way to advancement is through research or administrative work. Frequently, there is little or no check on college teachers to see how well they do their work. Because of the repetitive nature of this pursuit, the teacher may put forth great effort to organize and improve his courses, and yet, as far as student achievement is concerned, see little evidence of the fruits of his labors. Such a combination of circumstances may account, in part, for the enthusiastic

support given the seminars and for the lack of attention to these same principles in our graduate programs.

Supplemental training at the graduate level can vary widely. The direction in which it may be oriented is largely determined by the school, the interest of the instructor, and the needs of the students. For this presentation, examples will be drawn from colleges of pharmacy which offer both undergraduate and graduate work in pharmacology, and it will be assumed that both the instructor and the student are interested in teaching and research. As a matter of convenience, the discussion will be presented in three parts: seminars, teaching experience, and research experience.

Seminars

Several pharmaceutical educators have recommended special seminars of one type or another. The objectives of these seminars are usually twofold: to orient the student and to overcome deficiencies in his undergraduate background. For example, Martin and Sprowls[1] have described a seminar entitled "Graduate Orientation and Research Indoctrination" which covers the following 14 topics: (1) an introduction to the graduate program; (2) rules and regulations of the laboratory; (3) research in industry and in the university; (4) personnel demands for research in industry; (5) choosing a research problem; (6) the library and its use; (7) a survey of scientific literature; (8) planning and developing the research problem in industry; (9) planning and developing the research problem in the university; (10) statistics in research; (11) a brief survey of instruments used in research; (12) graphical representation of data; (13) writing for publication, and (14) oral presentation of the research paper. Although these subjects are excellent, they are not the only topics worthy of consideration, and are not necessarily the best ones for every institution or group of graduate students. The point to be emphasized, however, is that the seminar offers a valuable method not only for disseminating information which, as Dr. Drill mentioned, contributes heavily to the students' basic scientific and pharmacological training, but also to those areas in which they may be deficient.

We may encounter an occasional student or students, for example, who, despite the fact that they are at the graduate level, really do not know how to use the library. In our own institution we have invited the medical librarian to come in and conduct a seminar on the principles of library research. Not only was the librarian delighted to participate in this type seminar, but the students gained a great deal from his presentation. In another instance, we had a seminar on the writing of research papers and the principles of bibliographic citation. This particular seminar was conducted by Dr. Goodman and we all gained a great deal from it because of his extensive experience. I want to emphasize again that the opportunities for supplemental training through carefully planned seminars are governed primarily by the ingenuity of the instructor and the needs of the graduate student. The following are cited merely as examples: how to organize a department of pharmacology; how to develop and present a lecture for classroom presentation; how to plan and organize a laboratory in pharmacology; how to plan

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[1]Martin, A. N., and Sprowls, J. B. A course in graduate orientation and research indoctrination. Am. J. Pharm. Ed., 16, 247-250 (1952).

and construct an examination, and how to evaluate the progress of the student. If such an expanded seminar program is initiated, it may be desirable to invite speakers from other departments of the university to present selected topics. This should not only strengthen the program, but should also improve interdepartmental rapport. In any event, if carefully planned and energetically pursued, the graduate seminar can be a major educational experience.

Teaching Experience

Although the time available to the graduate student will not permit him to enroll in formal education courses, the basic elements of the learning process and the essential principles of good teaching can be presented in seminar fashion as previously mentioned. In addition, the undergraduate course in pharmacology, as presented in many colleges of pharmacy, offers an unusual opportunity for the graduate student to obtain practical experience in course and lesson planning, in constructing examinations, in laboratory instruction, and, eventually, in planning and presenting an undergraduate lecture. The alert instructor will take every advantage of these opportunities and will invite the graduate student to participate in all phases of the undergraduate program. At first this may only consist of sitting in on staff meetings concerned with course planning and with the problem of correlating the laboratory work with the lecture. Later, he should help plan examinations and should be given the responsibility of writing selected segments of them. All examination questions, including those written by the instructors, should be reviewed by the staff and graduate students prior to the test. This procedure will serve the dual purpose of eliminating those questions which are ambiguous and of teaching the graduate student how to write good questions.

Assisting in the undergraduate pharmacology laboratory can be another rewarding experience not only for the graduate student but also for the undergraduate students enrolled in the course. The graduate student will appreciate the opportunity to instruct in the laboratory and the undergraduate student will benefit by the presence of additional assistance. This activity, as well as all others connected with the teaching program, should be required of all graduate students and not limited to those fortunate enough to hold a teaching assistantship in the department. (At our institution we consider participation in the teaching program a part of the graduate student's education, and we make no distinction between those supported by research programs and those supported by teaching assistantships.) The confidence gained from explaining the usual elementary laboratory procedures and from answering student questions helps to prepare them for their next experience--classroom instruction at the undergraduate level.

After the student has completed his formal course work, and preferably during his last year of graduate study, the student should be invited to give a few of the lectures scheduled for the undergraduate course. This assignment should be made far in advance of the date at which the topics are to be presented. This will allow the student sufficient time to review the literature, prepare lesson plans, and to accumulate the desired teaching aids. The actual classroom presentation should be made in the presence of the instructor. I emphasize this because too frequently the only time the graduate student gets an opportunity to lecture

is when the instructor is called out of town. As a result, the instructor does not know how well the student presents the material and the student is deprived of the advice and counsel of the instructor. A conference following the lecture should consider not only the material presented, but also how effectively it was delivered. Attention should be given to appearance, speech, mannerisms, and other factors which may limit the student's effectiveness as a teacher.

Teaching opportunities of this kind will not make an experienced teacher out of every graduate student, but they will enable him to approach his chosen profession with more confidence. Furthermore, they may lead some students into a teaching career who otherwise might go into other areas of pharmacology.

Research Experience

Students taking graduate work in pharmacology should think of their lifetime occupation as one involving original investigation, whatever specific position is finally accepted. Therefore, the student should be encouraged to participate in some phase of research from the time he enters graduate school. Supplemental training of this type can be accomplished only if the faculties of colleges offering graduate work in this area are actively engaged in research and can interest the graduate student in some phase of these investigations. Initially, the student might be engaged as a research assistant and assigned some minor phase of an active research program. A modest stipend might even be paid for this work in order to encourage him to direct his free time to research activities rather than outside employment unrelated to future interests. As he gains experience and develops various technics, he should be assigned a research problem of his own. The problem selected should be rather discrete and hold forth the promise of possible publication upon completion. Such early experiences will not only orient the student into research procedures, but will also make it easier for him to arrive at a thesis problem. In addition, it alerts the student to possible avenues of research and trains him to recognize new, challenging problems.

Another plan which might be used to familiarize the graduate student with a wide variety of laboratory technics is referred to as "rotation research." This plan, introduced to the University of Utah by Dr. Louis S. Goodman, has the student spend three or four months on a part-time research project with each of three "specialists" in different areas of pharmacology. The sequence and the man with whom the student works is determined on the basis of student interest and approval of his major professor and the instructor concerned. The following example will illustrate how this plan operates in the Departments of Pharmacology at the University of Utah College of Medicine and College of Pharmacy. Upon completion of his major course requirements, the graduate student usually knows the staff personally and has a fairly good understanding of their research interests. The graduate student indicates to his major professor his research interests and the instructor with whom he would like to work. Arrangements are then made for the student to spend a specified time with the instructor selected; this might be a man working in the area of cardiovascular pharmacology. Upon the completion of this project, he selects another professor in a different area, such as neuropharmacology. Finally, he may spend a similar period of time working with a man, perhaps in renal pharmacology. It should be emphasized that the professor does

not set up new problems, but the student assumes the responsibility of learning the technics and pursuing some facet of the research currently underway. In general, most students work in about three different areas either prior to or during the time they are working on their thesis problem under the direction of their major professor.

Although a research program similar to that described can be introduced only in those schools closely allied with a department of pharmacology in a medical school, some modification of it should prove effective. For example, a rotation plan might be worked out between closely related departments, such as the departments of pharmacology, physiology, bacteriology, and experimental biology. The ultimate success or failure of the rotation plan, however, depends upon the presence of an active research program and good rapport with cooperating departments and individuals.

In conclusion, it should be stated that there are many other methods by which supplemental training can be introduced at the graduate level. It should be emphasized that the examples cited are merely representative of the ways in which this type of training can be implemented. Further thoughtful consideration of this problem may reveal other and even more effective teaching devices which can be used to overcome the known deficiencies in present day graduate education.

THE DEVELOPMENT OF A PHARMACOLOGY RESEARCH PROGRAM

John Emerson Davis

University of Texas

My topic seems to allow me considerable latitude and longitude in what I may say. At the outset, I should like to emphasize that there are no set rules prescribing the manner in which a research program should be established. This is as it should be, since the principle of academic freedom applies to research as well as to teaching in the universities and colleges.

A program may be defined as a "plan to be followed." A pharmacology research program can be a short-term plan for a single investigation, or a long-term program (schedule) of work intended to cover perhaps a period of years. It seems that a variety of short-term programs are undertaken in most pharmacy schools. On the other hand, a number of pioneer pharmacologists have built great reputations through prolonged and intensive work on certain classes of drugs which produce certain types of action: e.g., Cushny on diuretics, Cannon and Abel on epinephrine, Hunt and Dale on choline esters, Harry Gold on cardiac drugs, etc. Even today, we have laboratories which are engaged in long-term programs of specialized pharmacologic research. The University of Michigan Pharmacology Department has worked on various problems but consistently continues to make studies on the narcotic analgesics. Dr. Way, at California, also has done much fine work on analgesics. Drs. Swinyard and Goodman, at Utah, have continued their excellent contributions in the field of anti-epileptic drugs over quite a period of years. These are only a few of a number of examples that might be cited.

Our topic might also allow us to emphasize the word "development," so that we might paraphrase the title to read: "Ways and Means of Developing Pharmacology Research Activity." This is not a problem for the deans, but for the professors of pharmacology. We may therefore devote our attention to the kinds of research programs that may be developed, and also to the subject of "how" to promote research activity.

The development of a research program in pharmacology obviously requires personnel, chemicals and drugs, equipment and apparatus, and animals. The personnel, or people who perform research experiments in pharmacology ought to comprise the faculty and graduate students in a department of pharmacology. Ideally, the professor and senior faculty members should be people with good training and considerable research experience with a goodly number of research publications to their credit. I believe that they should also strive to become members of the American Society for Pharmacology and Experimental Therapeutics, which is the leading professional society in this field in America. The graduate students who work in this field should, naturally, have had suitable formal courses in pharmacology, physiology, and chemistry as prerequisites essential to the conception and execution of a research problem.

With regard to equipment and apparatus, it seems that the usual standard equipment of a physiological or pharmacological laboratory should be available, and that special tools and apparatus which are required for special problems should be ordered as needed insofar as the school or departmental budget will permit.

Good animal quarters are very important for most research programs. We keep certain animals in stock continuously, including rats, mice, and rabbits. We have dogs and frogs most of the time, and we order guinea pigs, pigeons, and chickens as we need them. Most of the rats, mice, and rabbits used in our college are bred in our own animal quarters. Then we also have students, who make very good subjects for some experiments. They require no special care, but of course the investigators must be careful to confine the use of human subjects to safe procedures and to medication which is not dangerous. Recently, we used students to demonstrate the erythropoietic action of cobalt and the production of polycythemia in humans. Except for occasional pimples on the face and slight headaches, there were no ill effects!

There are many different ways in which to develop a research program, and there are certainly different kinds of research programs. Some professors prefer to sit at a desk and guide their students by remote control from an armchair, while others may work with the students in the laboratory. There are other professors who may work half the night or all night on their own research thus setting a shining example, and perhaps adding a competitive stimulus, to challenge the younger people to work harder. I believe that there is a happy middle ground in which the student receives a little help in the laboratory, but receives more by way of advice and criticism in conferences at the professor's desk.

It seems to me that there are two general types of research programs. One type involves specialized research on certain classes of drugs or certain physiological processes or systems which are affected by drugs, or the development of drugs for treating definite diseases or abnormal conditions. This type of program may continue for many years and, when fruitful, may be more likely to build lasting reputations for the individuals or laboratories involved in the work. The other general type of program might involve a wide variety of diverse research investigations which are embarked upon according to the investigator's interest or his conception of the ideas. There are certainly advantages to either type of research program, whether it be (1) specialized in a narrow, rather limited field or (2) variegated. The latter type, while possibly less likely to build a wide reputation for the worker, should presumably give its adherents more first-hand acquaintance with more of the phases and methods of pharmacology. Theoretically, it should make the worker a better all-round pharmacologist.

Obviously, either type of research program may obtain for the individual scientist, or for the whole department or laboratory of pharmacology. I do not believe in confining a whole laboratory to a specialized field of pharmacologic research, especially in a college or university. Such an event is not likely to occur in pharmacy schools.

Collaborative research involving two or more individuals is to be commended provided each of the participants agrees to the arrangement and has an active part

in the brain work as well as the routine work of the experiment. Compatibility among the workers is essential to good work, and sometimes it is lacking. I have seen collaborators break up after a session of harsh words, or sometimes "a profane silence." If certain individuals cannot work together, they should work separately. It is my opinion that most of the great ideas are conceived by individuals, not by groups of people. Although a team of investigators can collect more data than a single individual in a given period of time, there is still great virtue in the individual workers, many of whom will make great contributions and discoveries.

The screening of new chemicals for pharmacological activity is not, in my opinion, a promising field of activity for the university laboratories, unless the latter have access to newly-synthesized chemicals prepared at their own institutions. Screening tests are more easily performed in the industrial laboratories which employ people for this kind of work in which they have a financial interest. I believe that, in particular, the routine pharmacologic testing of impure plant extracts is usually a waste of time for a research-minded pharmacology department, because much work may be expended without a good percentage yield of positive results. It is true that pharmacy schools offer good opportunities for collaborative work between pharmacologists, pharmacognosists and chemists, but any such work should be mutually profitable to all groups. No one group should ever become a "service department" for another. Some years ago, I was assigned a graduate student by an administrator. Without my knowledge, the student had also been assigned a problem which required him to isolate the active ingredient from a plant (for the first time), and to then make a complete pharmacological study of the same. This did not seem a suitable problem for a master's degree, so we decided upon another problem which seemed more feasible and more interesting. I like to have a student enjoy his research, especially his first experience with it, and I try to help him pick a problem which offers a reasonable chance of giving some positive results.

Every graduate school professor has met young graduate students who come in with a desire to solve certain problems which have challenged solution by experts for many years. Of course, they often have no idea as to how to solve the problem, and frankly the professor may also be at a loss as to how to approach the problem. Sometimes methods or tools are not available even if ideas are present. We have all seen students who have an abundant imagination but little touch with the reality and the practical aspects of research. An occasional student seems to have a flowery picture of research in which he imagines that it is only necessary for him to step into the laboratory for a brief half-hour, snap his fingers or shake a test tube, and come out with a brilliant new discovery which will entitle him to an armchair job as a research director. Such a student needs to be "brought down to earth" and made to realize that hard work and "elbow grease" are usually necessary to gain the privilege of making a single new scientific conclusion, which may be capable of being summed up in ten words or less.

Graduate students, and sometimes teachers in their early years, are amazed to find that they may experience a little difficulty in finding or "hitting upon" a good original research problem. As everybody knows, the ideas for research investigations are often acquired as the result of reading books and journals in the pharmacological and related fields. In addition, during the course of the

work on a research problem in the laboratory, it frequently happens that new problems are "opened up" or reveal themselves, and it is then sometimes profitable to pursue the new ideas or, as it were, "to follow one's nose." Another challenging source of stimulation for research investigation is the occurrence of poisoning by chemicals for which there are no specific pharmacologic antidotes. Of course, this stimulation is more real for those who work in or near a hospital and who see these poisoning cases first hand. In medical schools especially, one may also see diseases for which there are no cures or for which treatment is unsatisfactory, and this experience can at least imbue one with the desire to do something about it. A more unusual way in which one may start a research problem is to become involved in a court case as an expert witness for the prosecution or the defense. If certain scientific matters are obscure, it may behoove one to go to work in the laboratory in search of the answers, and thus to become more "expert" perhaps with a view to being able to dominate the lawyers. However, such action is no assurance that everything will go smoothly in the court-room--because there are some judges who will severely restrict the sphere of the testimony and even threaten one with contempt of court. The author speaks from experience.

For purposes of discussion, we might ask the question, "Why develop a research program?" I have heard professors say, "research is just a hobby," or it is "just a thing that runs hot and cold, and you'll cool off sooner or later." Then there is the old frequently-heard statement that "research men are poor teachers," a sentiment which usually is voiced only by persons who have never performed any original research in their lives. There is also, unfortunately, the fact that there are some academic institutions in which the achievement of meritorious research results is not rewarded in any material way, and one may gain just as rapid advancement by not engaging in research. This is probably not true of the better universities. In answer to these arguments, I would say that research should be something more serious than a hobby, but that if it can be enjoyed with the same pleasure that a hobby affords, then that is all to the good. The stimulation and definite knowledge of certain facts that are gained through research activity should, by and large, make the investigator a better teacher than the noninvestigator. As for financial reward, very few of us can show disdain for money, but the achievement of research results usually gives the author considerable personal satisfaction and pride in what he has done. This kind of reward is not entirely intangible. The question as to whether teaching alone is a full-time job is a delicate question. I would say that it is not. At least I would not feel that my life had been fully lived if it had been devoted solely to teaching. Most of us need to feel that we have accomplished something with our own hands and talents, in addition to disseminating knowledge to the young. I am sure that all of you who have made new contributions to knowledge have experienced the thrill that comes from making a new scientific discovery, be it large or small. For us, it is certainly more exciting and more creative than, for example, selling shoes or real estate. (There is also the possibility of someday earning an honorary degree, and other forms of tangible recognition.)

At the University of Texas at Austin, our research in pharmacology has consisted mainly of that done by the professor and various graduate students. For many years, I have worked on problems concerned with the pharmacology of erythropoiesis, or the effects of drugs on the blood and bone marrow--and this continues to be my principal field of interest. However, I do not try to influence my

students to work on hematological problems. In fact, I try to steer them into problems of an entirely different nature. Actually, I try to get the student to conceive a problem of his own. Then, together, we consider the problem from the standpoint of feasibility, equipment requirements, estimated time necessary for its completion, and the possibility of learning some significant new facts. However, it frequently happens that the graduate student cannot think of a suitable research problem. In this case, I try to suggest two or three possible problems and allow the student to select one. This avoids the necessity for the assignment of a problem, which I would consider a poor academic practice.

Our program at Texas may be illustrated quickly by listing the research investigations completed at our laboratory during the past five years, which include the following titles:

Anemia produced in rats by paraphenylenediamine.

Polycythemia induced by phenylephrine HCl.

The production of an experimental anemia in guinea pigs by the administration of acetylcholine.

The effect of fat-feeding on the duration of Thiamylal anesthesia.

The modifying effect of chlortetracycline on the normal response of the frog heart to adrenalin.

Cobalt polycythemia in chickens.

Cobalt polycythemia in normal human subjects.

Effects of the daily administration of histamine in a sustained release form on the formed elements of the blood of mongrel dogs.

Studies on the effects of anticholinesterases on the permeability of physiological membranes.

A perusal of the foregoing list will show that we have continued a specialized program of study on the effects of chemicals on the blood, but that we have interspersed various other unrelated problems into our program.

I think that it is an excellent plan for an individual, or perhaps a collaborating group of individuals, to have a long-term specialized research interest (or program) in a particular field of pharmacology. This does not, by any means, prevent the individuals from undertaking diverse problems of an entirely different nature as occasion and opportunity may beckon. Indeed such changes of program may prove refreshing and scientifically profitable. A program does not have to be a set, binding, irrevocable schedule which does not permit deviation or change.

A specialized program, furthermore, does not have to be planned at one time for an ensuing number of years. In fact it is better not to try to plan it too far ahead, because new developments or other research workers may encroach upon

the plan or obviate the necessity for some of the planned work. I have worked "off and on" upon the subject of cobalt polycythemia over a period of nearly twenty years. Although we have not established the mechanism of the action of cobalt, we have determined many interesting facts in connection with it, and we still hope to learn exactly how cobalt stimulates the bone marrow. Before you decide that I am exceptionally slow in this work, let me hasten to add that I know at least three other men (good scientists), each of whom has worked intermittently on this same subject over a similar period of about twenty years. Naturally, we have all investigated other subjects according to our personal interests.

Actually the term "development" has been defined as a "gradual unfolding" and as "growth." Therefore, I could have spent the whole time in telling you of the development of my own research program which has followed a logical and interesting sequence. However, I did not believe that the Seminar intended to have me do this, and so I have refrained therefrom.

Departmentalization in pharmacy schools would, I am sure, help to facilitate the development of research programs in pharmacology. It might also help to improve the spirit of the faculty. At Texas, we are not departmentalized, although original plans had called for it five years ago. Perhaps financial considerations are the main deterrent to departmentalization in many of the colleges of pharmacy.

Our graduate school program might be enlarged if we would accept well-prepared graduate students from other divisions of the university. Higher degrees in pharmacology are open <u>only</u> to Pharmacy College graduates at the University of Texas.

Attendance at scientific meetings is beneficial to all who are interested in pharmacologic research. Aside from the A.Ph.A. meetings, there are many other very excellent meetings, such as those of the Society for Pharmacology and Experimental Therapeutics, the Federation of American Societies for Experimental Biology, and the A.A.A.S. By the same token, the publication of research results need not be confined to the <u>A.Ph.A. Journal</u>, but might well be dispersed to other excellent journals, some of which may be preferred over the <u>A.Ph.A. Journal</u> by most pharmacologists. For example, the <u>Journal of Pharmacology & Experimental Therapeutics</u>, the <u>Proceedings of the Society for Experimental Biology and Medicine</u>, and for some articles the <u>American Journal of Physiology</u>, are a few excellent journals which are accessible to pharmacologists. It seems to me that pharmacy school faculties in our field might gain wider notice of their work by occasional publication in some of these journals.

Summary

We have discussed certain matters pertaining to the development of research activity, the ways of finding or selecting research problems, and the two general types of pharmacology research programs that are readily apparent.

I believe that an ideal plan is to promote a long-term specialized program in a particular field of pharmacology, but to participate in short-term variegate

programs from time to time as one's interest dictates. This promotes the acquisition of both depth and breadth of knowledge.

It is my opinion that the creation of more pharmacology departments in the colleges of pharmacy would greatly facilitate research in this field. Such departments should be allowed to offer the work for higher degrees to any qualified graduate students, not just graduates in pharmacy.

FINANCIAL SUPPORT FOR RESEARCH

Dale R. Lindsay[1]

I have been asked to discuss with you the financial support for research available through the research grants and fellowship programs of the Public Health Service. Rather than try to cover all aspects of these programs in this brief talk, I have distributed copies of two recent papers[2] which give a statement of the various aspects of the research grants and fellowship programs of the Public Health Service more succinctly than I could from this podium. I would like to elaborate a bit upon some parts of the program which I think would be of especial interest to you and which are referred to only briefly in Dr. Allen's paper, Methods Employed by the Public Health Service to Increase the Number of Productive Investigators and Research Teams.

The major objectives of the programs are (1) to expand research activities throughout the country; (2) to provide on-the-job training for scientific personnel in connection with the research being conducted; (3) to stimulate the initiation of research in small institutions where previous research programs have been very limited or nonexistent, and (4) to encourage investigators to undertake research in neglected areas needing exploration. Neglected areas, I might add, may be interpreted to mean geographic areas as well as scientific areas.

It is appropriate that I bring to the attention of this group Item 4, concerning neglected areas, inasmuch as one research area heretofore neglected should be of particular interest and significance to pharmacologists. I refer to the problem of possible toxicities of food additives of all kinds. All of us today are constantly exposed to both intentional and adventitious food additives. I won't attempt to describe to you something that you know far better than I, but I want you to know that the need in this area has been recognized and that several federal agencies are trying to stimulate people such as yourselves to undertake this type of research.

The greatest shortage that we face in the development of extramural research grant programs is that of manpower. In an attempt to relieve this shortage, the research fellowship program and the training grants program have been developed. A brief explanation of these programs is included in the papers you hold. In the past, training grants have been limited more or less to clinical fields primarily of interest to one or the other of the seven categorical institutes. At

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[1]Assistant Chief, Division of Research Grants, National Institute of Health, Public Health Service, Department of Health, Education, and Welfare.

[2]Dale R. Lindsay: Public Health Service Grant and Award Programs: General Information. July 19, 1957. See p. 215.
Ernest M. Allen: Methods Employed by the Public Health Service to Increase the Number of Productive Investigators and Research Teams. July 9, 1957. See p. 219.

the last session of Congress, legislation was passed which would give the Division of Research Grants authority to make training grants in other areas, primarily basic research areas in the preclinical sciences, and some to foster experimental design in anesthesiology. Unfortunately, the funds to implement this new program have not been forthcoming. A modest beginning can be made, however, with funds generously allocated for this purpose by the categorical institutes which have funds earmarked for training purposes. The ground rules have not yet been established, but in all likelihood the grants will be limited the first year to schools of medicine, dentistry, and osteopathy. We hope that in successive years graduate schools of all types will be eligible for these grants. One of the primary fields in basic or general research training grants will be that of pharmacology. Thus, if any of you have problems which could be solved or bettered by a training grant, we urge you to make application.

It might be helpful to mention a few of the items that can be included in a training grant. Faculty positions that may be necessary to augment or permit an accentuated or expanded training program, equipment necessary to provide training, and stipends for trainees can be paid by a training grant. The level of stipends varies, being determined by the level of similar stipends normally paid at the grantee institution.

I think that perhaps the best way to be sure of covering the points of greatest interest to you, is for me to conclude my remarks and allow you to ask questions, which I will endeavor to answer.

Dr. Webster: Are there questions from the audience?

Dean Rowe: On these requests for grants, is there usually quite a delay before you get an answer? We have a grant request pending, I think since last April, and we haven't received an answer yet. We have a person we can put on in September and presumably we aren't going to hear until September. Is there any way we could be informed earlier whether the decision is negative or affirmative about the grant being awarded?

Dr. Lindsay: We appreciate the position in which you find yourself and we wish there were something we could do to let you know earlier. It takes a minimum of four months to get an application through the regular procedures of review and award. The only thing I can suggest to minimize such situations is that you obtain additional research grants from various sources to provide fluidity in your program and funds to carry the program while you wait for the answer on any particular grant.

In order that you may understand why it takes so long to have an answer on your application, let me describe briefly the procedure involved. When a research grant application is received, March 1, July 1, or November 1 (the deadlines for receipt of applications to be reviewed at the next Council meetings) the first action on the part of the Division of Research Grants is to determine which study section should receive it for study and appraisal and which institute should receive it for further review and recommendation of payment or disapproval. Sometimes several thousand applications are received within a few days and it may take two weeks to process these and assign them to the proper reviewing bodies.

Once these are assigned to the 27 study sections and the one standing committee, the executive secretary of each study section mails copies of them to the members of his study section, preferably six weeks ahead of its meeting, so that the referees who have been assigned to the review of the applications have adequate time to do the literature search that may be necessary, and to confer with colleagues in this field of research.

The study sections meet three times a year, and here the referees present the applications to the other members of the study section, who have studied them also but not necessarily in the same detail. Each application is discussed at the meeting, voted upon, and given a priority score (1 for a "perfect application" to 5 for the lowest priority) by each member of the section. The collective opinion is written and is sent, along with the averaged priority score, to the Council already selected. The Council members like to have at least a month before they have to act on an application. This month gives them time to ask questions with regard to policy, to iron out disagreements, to obtain additional information, etc. The Council makes the final recommendation to the Surgeon General, who awards the grant.

The procedures I have described represent a truly democratic process, and any democratic procedure is inherently slow. I believe, however, that you would agree with me that your applications receive a better review and are awarded on a more equitable basis through this procedure than they would through some other potentially faster but necessarily bureaucratic procedure.

Dean Orr: I wonder if you could tell us some of the characteristics of the "perfect application"?

Dr. Lindsay: The criteria for a "perfect application" would vary from study section to study section, depending upon the disciplines and the personalities involved. In general, the objective must be worthwhile, but if the methodology set forth would not allow the attainment of it, the high quality of the objective would have little influence upon whether or not the application were approved. A good application requires the development of a protocol in which the specific aims and the methods proposed in achieving these aims are set forth. The significance of the proposed research should be pointed out, and please do not interpret this to mean clinical significance. Direct application does not need to be foreseen. We do have to stay within fields that are fairly closely allied to health and medicine, but we support some very basic research in biochemistry, biophysics, physiology, morphology, genetics, and similar fields.

In writing an application, some people have difficulty in making out the budget sheet, and ask, "How can one say just how much he is going to spend on any one item?" The budget sheet is primarily for the purpose of letting the study section know whether or not the applicant can visualize what it would take to do a piece of research. These are experienced research men, well versed on the cost of such research. Once in a while the study section actually recommends an increased amount of money based upon this knowledge of need and we have to write to the investigator to ask if he will accept it. I don't recall any time when this has been turned down!

A little over a year ago the policy regarding budgetary items was liberalized to conform with the long-established liberal policy of allowing complete freedom to the investigator with regard to changes of direction or conduct of research. After the grant has been awarded, the grantee is free to rearrange budgetary items as he sees fit. Only two restrictions upon the budget are now in effect: (1) research grants may not be used for "four-wall" construction, though they may be used for renovation or remodeling of research quarters; (2) research grants may not be used to attend foreign meetings, though there is no restriction on foreign travel if the investigator feels that that would enhance his research. On occasion, requests to use grant funds for the purpose of attending a foreign meeting have been granted, but special permission from the Council concerned must be obtained.

Dr. Webster: Does it have to be specified in the budget that you are going abroad?

Dr. Lindsay: No, this can develop in the course of the research. Sometimes, however, I think that specifying that you are going to visit laboratories and work for a short period of time abroad strengthens the application, and if you know this, it should be stated.

Dr. Webster: We do run into difficulty locally, however. Even though the grant would permit it, our own university controller would not permit it unless it were forecast in the original budget.

Dr. Lindsay: This is an interesting point. We have observed over the years that most of the limitations placed upon the expenditure of research grant funds have been imposed by the universities themselves, not by the federal government. We are trying to make the least possible imposition of bureaucracy upon research workers.

Dr. Way: A point of information on fellowships. I notice that they are awarded to schools of medicine, dentistry, and public health. Does this include schools of pharmacy if someone wants to do postdoctoral studies in a school of pharmacy?

Dr. Lindsay: Yes, he could be awarded a postdoctoral fellowship for study in a school of pharmacy. The senior research fellowship grants to foster research in the preclinical sciences and the part-time research fellowship grants for predoctoral students are the only fellowships which are restricted to the schools of medicine, dentistry, and public health. These fellowships are not yet available for schools of pharmacy but all other fellowships, either undergraduate or graduate, are as available for schools of pharmacy as for any other school.

PUBLIC HEALTH SERVICE GRANT AND AWARD PROGRAMS

GENERAL INFORMATION

Dale R. Lindsay, Ph.D.[1]

The Public Health Service is charged with the responsibility for conducting and supporting research into the causes, diagnosis, prevention, and treatment of diseases and disabilities of man. In addition to the extensive research conducted in Government laboratories, the Service provides support of research and training in non-Government institutions.

The Division of Research Grants of the National Institutes of Health has administrative responsibility for the management and policy direction of the Public Health Service research grants program. The appropriations and programming responsibilities fall in the following eleven categorical Institutes and Divisions of the Public Health Service:

National Cancer Institute, National Heart Institute, National Institute of Allergy and Infectious Diseases, National Institute of Arthritis and Metabolic Diseases, National Institute of Dental Research, National Institute of Mental Health, National Institute of Neurological Diseases and Blindness, Division of Hospital and Medical Facilities, Division of Nursing Resources, Division of Sanitary Engineering Services, and Division of Special Health Services. Noncategorical or general research grant funds are available from the Division of Research Grants for scientists whose interests do not fall within the scope of responsibility of the Categorical Institutes and Divisions.

Although a very small research grant program was supported by the National Cancer Institute following the passage of the National Cancer Act in 1937, it wasn't until the close of World War II in 1945 that the present across-the-board research grant program was born. Agreement was then reached that responsibility for approximately 50 research projects should be transferred to the Public Health Service from the Office of Scientific Research and Development, and that the Division of Research Grants should be established to administer the program.

During the period 1946 to 1950, the Congress authorized the above-mentioned categorical Institutes, following the general pattern of the National Cancer Institute. In each instance, provision was made for research to be conducted within the facilities of the Institute, for research grants and fellowships to nonfederal scientists, and for other types of academic and research training.

By Congressional authority, nine National Advisory Councils have been established as advisers to the Public Health Service. No research or training grant may be paid by the Surgeon General unless recommended for approval by one of these Councils. Seven of the Councils advise the seven Institutes of the National Institutes of Health on their respective programs, in addition to reviewing

[1] Assistant Chief, Division of Research Grants, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare.

and recommending appropriate action on applications for grant support. The National Advisory Health Council reviews applications for general or noncategorical research grants not falling within the interest of the Institutes, and advises the Surgeon General on matters relating to health activities and functions of the Service. The Federal Hospital Council advises the Surgeon General on matters relating to the administration of the Hospital Survey and Constructions Program and reviews applications for grants in aid of projects in research, experiments, or demonstrations relating to the development, utilization, and coordination of hospital services, facilities, and resources.

The National Advisory Council on Health Research Facilities, established in July 1956, reviews and recommends appropriate action on applications submitted by universities or other nonprofit institutions for assistance in the construction and/or equipping of additional facilities for the conduct of research in the sciences relating to health.

In view of the large number of applications which must be evaluated, covering the entire range of medical and biological research, the Division of Research Grants has established 27 Study Sections of special consultants expert in various fields of research. These study sections act as technical advisers to the National Advisory Councils and to the Surgeon General. They accept responsibility not only for providing technical advice on applications for research support but also in conjunction with the Councils, for surveying as scientific leaders the status of research in their particular fields in order to determine areas in which additional activity should be initiated or expanded.

Brief functional statements for the principal types of grants and awards made by the Public Health Service in support of research, training, and construction are shown as follows:

1. Research Grants - Research grants are made to universities, hospitals, laboratories, and other public or private institutions and to individuals for support of research projects in health, medicine, and allied fields, including experiments, or demonstrations relating to the development, utilization, and coordination of hospital services, facilities, and resources. The major objectives of the research grant program are (1) to expand medical and biological activities in research institutions throughout the country, (2) to provide on-the-job training for scientific personnel in connection with the research being conducted, and (3) to stimulate new investigations in fields needing exploration. These funds provide for salaries, equipment, supplies, travel, and other expenses such as renovation and alteration of existing facilities, reprints, hospitalization.

2. Research Fellowships - Five types of research fellowships are available: (a) Predoctoral Research Fellowship, awarded to qualified persons who hold a Bachelor's degree or equivalent training. Fellows are expected to carry on studies oriented toward graduate training in fields related to the health sciences. (b) Postdoctoral Research Fellowship, awarded to qualified persons holding a Doctor's degree in medicine, dentistry, or related fields. Stipends and extra allowances are awarded under established Public Health Service policy. (c) Special Research Fellowship, awarded to qualified applicants who have demonstrated unusual

competence for research, or who require specialized training for a specific problem. The amount of the stipend is set in each case. (d) Student Part-time Research Fellowship, designed to give students in medicine, dentistry, nursing, and public health, an opportunity to explore the research field in the hope that many of those supported will enter into full or part-time research careers. A predetermined number of these Fellowships may be awarded each year. (e) Senior Research Fellowship, granted in support of preclinical science investigators between the completion of postdoctoral training and eligibility for permanent academic appointment. These funds provide for salaries plus research expenses not exceeding $2,000. The Senior Research Fellows may also apply for research grants to support their research.

3. Undergraduate Training Grants - Undergraduate training grants are awarded to medical schools, dental schools, public health schools, and schools of nursing to assist in developing expanded and better integrated undergraduate instruction in the special fields concerned. It is the responsibility of the institution to determine the most appropriate use of the funds.

4. Graduate Training Grants - Graduate training grants are awarded to public and private nonprofit institutions interested in providing special training for researchers, teachers, and prospective practitioners interested in public service. These funds may be used to improve facilities and to provide salaries for faculty, staff, and trainees, along with necessary supplies and materials.

5. Traineeships - A series of traineeship stipends are awarded either directly to the individual in training or through a training grant to the institution for this purpose. Traineeships are awarded to physicians and other professional personnel in order to encourage specialization in one of the branches of medicine supported. Stipends and extra allowances are made under established PHS policy.

6. Health Research Facilities - Under the Health Research Facilities Act, July 1956, the Congress authorized the establishment of a program to assist in the construction and/or equipping of additional facilities for the conduct of research in the sciences relating to health by providing grants in aid on a matching basis to public and private nonprofit institutions. The amount of Federal funds awarded may not exceed 50 per cent of the total costs of the research portion of the facility, the remaining sum to be provided from nonfederal sources.

Public Health Service programs in support of research and training in universities, hospitals and other nonfederal institutions has justified continued Congressional interest, as evidenced in the following table which shows the growth of the programs by appropriation year:

	Research Grants	Fellowships	Training Grants[1]	Health Research Facilities
1946	$ 780,000	$ 44,000	$ 29,000	$ ---
1947	3,576,000	178,000	250,000	---
1948	9,145,000	520,000	2,810,000	2,303,000
1949	10,871,000	1,115,000	3,930,000	---
1950	13,065,000	1,448,000	6,415,000	5,775,000
1951	16,713,000	1,565,000	6,928,000	9,459,000
1952	18,173,000	1,755,000	7,392,000	4,625,000
1953	20,374,000	2,024,000	8,194,000	---
1954	28,866,000	2,133,000	10,813,000	---
1955	33,918,000	2,562,000	11,051,000	---
1956	38,038,000	2,800,000	14,502,000	---
1957	93,300,000	5,397,000	28,075,000	30,000,000
1958	101,265,000	6,812,000	32,560,000	30,000,000

[1] Includes traineeships.

July 19, 1957

METHODS EMPLOYED BY THE PUBLIC HEALTH SERVICE TO INCREASE THE NUMBER OF PRODUCTIVE INVESTIGATORS AND RESEARCH TEAMS

Ernest M. Allen, Sc.D.[1]

I. Research Grants

The Public Health Service supports research projects initiated by individual scientists or groups of scientists located for the most part in professional schools. Grants may be made to universities, hospitals, laboratories, and other public or private institutions and to individuals for support of investigations in health, medicine, and allied fields. Research grants are intended primarily to support biological and medical research projects, either laboratory or clinical in nature. Occasionally, however, support is provided for surveys and other special projects where the end product will facilitate or expedite the conduct of biological or medical research.

The major objectives of the program are (1) to expand research activities throughout the country, (2) to provide on-the-job training for scientific personnel in connection with the research being conducted, (3) to stimulate the initiation of research in small institutions where previous research programs have been very limited or nonexistent, and (4) to encourage investigators to undertake research in neglected areas needing exploration.

In most cases the Public Health Service supports research initiated by the scientists, but in some cases special programming is required. In such instances, responsible staff and members of advisory groups will collaborate in the stimulation of additional research on a given problem or aspect of a problem. Quite often such stimulation involves finding investigators with natural interests, who are willing to undertake additional research, often involving simply an extension of current work. A good example is the emphasis now being placed on cancer chemotherapy.

It has been estimated that 14 per cent of the total of the research grants provides training of professional and nonprofessional staff. The types of training afforded are varied; for example, the funds may be used to pay stipends for part-time students, graduate students, students who drop out of school for a year in order to get specialized on-the-job training, and for the research fellow or associate who is learning to do independent research under the guidance of a senior scientist.

Research grant funds may provide for salaries, equipment, supplies, travel, and other expenses necessary to the conduct of the research. The investigator has essentially complete scientific and budget freedom. There is no limitation on the number or size of grants that may be made to any one investigator or to any one institution in a fiscal year, nor is there limitation on the number of years a specific project may be supported.

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[1]Chief, Division of Reserach Grants, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare.

July 9, 1957

The research grants program constitutes by far the largest program of Public Health Service awards, in terms of both money expended and number of institutions affected. In Fiscal Year 1957, approximately 6,000 research grants have been awarded in a total amount of $80,000,000.

II. Research Fellowships

Research fellowships are intended to increase the number of scientists qualified to carry on independent research. Seven types of fellowships are presently available:

(1) Predoctoral research fellowships are awarded to students with a bachelor's degree or equivalent, for the pursuit of graduate research training in the fields related to the health sciences. Stipend rates are $1,600, $1,800, and $2,000 for the first, second, and third year, respectively. Allowances for dependents, travel, and tuition are added to the stipend.

(2) Postdoctoral research fellowships are awarded to qualified persons holding a Doctor's degree in medicine, dentistry, or related fields. Stipend rates are $3,800, $4,200, and $4,600 for the first, second, and third year, respectively. Allowances for dependents, tuition, and travel are added to the stipend.

(3) Special research fellowships are awarded to qualified candidates who have demonstrated unusual competence in research or who require specialized research training. The stipend, including extra allowances, is determined at the time of the award.

(4) Student Part-time Research Fellowship Grants are awarded to schools of medicine, dentistry, nursing, and public health. The awards are designed to give students in the health sciences an opportunity to explore the research field in the hope that many of those supported will enter into full or part-time research careers. Units of $600 are provided for part-time research work during the school term, or for full-time research work for 2 months during any time when curriculum work is not scheduled for the student.

(5) Senior Research Fellowship Grants are awarded to schools of medicine, dentistry, and public health in support of competent scientists who wish to conduct research and teaching in the preclinical sciences. These fellowships provide support between the completion of postdoctoral training and the time of eligibility for appointment to permanent or higher academic posts. The awards are made for 5-year periods, renewable, and provide for salary, plus partial research expenses not exceeding $2,000. Senior Research Fellows may also apply for additional support for their research needs.

(6) Post-Sophomore Research Fellowship Grants are awarded to schools of medicine and dentistry for support of students who wish to obtain research training prior to completion of their professional degrees. Participants must be willing to drop out of regular courses for one, two, or three years. The stipend is set by the school in amounts not to exceed $3,200 annually. Allowances for dependents and tuition are added to the stipend.

(7) Foreign Research Fellowships are awarded to a limited number of scientists who wish to study in United States laboratories. The purpose of the program is to provide an opportunity to strengthen medical research by mutual exchange of research methods, scientific philosophy, and cultural values. Nominations will be made by respective National Research Organizations in each Western European country. Candidates must have (a) completed a doctoral degree in one of the medical or related sciences, and demonstrated proficiency in research, (b) made satisfactory arrangements with the laboratory in the United States where training will be obtained, and (c) acquired a workable reading and speaking knowledge of the English language. Scientists will be brought to the United States on an exchange-visitor's visa, which requires return to the homeland for a period of at least two years at the end of the training period. Stipends are $3,800 for the first year and $4,100 for the second year. Dependency, travel and certain other allowances are added to the stipend.

In Fiscal Year 1957, over 2,000 research fellowships were provided in a total amount of $5,300,000.

III. Training Grants and Traineeships

Training grants are intended to augment the nation's supply of qualified scientific investigators by assisting in the establishment, expansion, and improvement of training and instructional programs in universities and other institutions. Aid to the institution is provided by grants in two general classes--undergraduate and graduate.

Traineeships to individuals may be awarded either through one of the graduate training grants or directly to the individual in training. Traineeships are intended to increase the number of qualified investigators by encouraging advanced training in specialized areas of medical and related research, as well as in the fields of public health and nursing. Stipend rates vary according to the nature and requirements of the different fields covered.

(1) Undergraduate training grants are awarded to schools of medicine, dentistry, nursing, and public health to assist in developing expanded and better integrated undergraduate instruction relating to the prevention, diagnosis, and treatment of cancer, mental illness, and cardiovascular diseases. It is the responsibility of the institution to determine the most appropriate use of the funds.

(2) Graduate training grants are awarded to public and private nonprofit institutions interested in providing special training for researchers, teachers, and prospective practitioners interested in public service. Funds may be used to improve facilities and to provide salaries for faculty and staff, stipends for trainees, and necessary supplies and materials.

In Fiscal Year 1957, over 1100 training grants have been made in a total amount of $25,000,000. Approximately 1,950 trainees were supported under these grants. In addition, 405 direct traineeships in a total amount of $1,857,000 have been made.

THE IMPORTANCE OF PROFESSIONAL AFFILIATION TO A GRADUATE STUDENT IN PHARMACOLOGY

James M. Dille

University of Washington

In speaking about this subject I would like to recall something Dean Lyman said on some long-forgotten occasion, "A man can be religious and not go to church, but if a man is truly religious he will inevitably affiliate with some church." So let me say that a person can do research in pharmacology alone and in isolation, but if he is truly a pharmacology researcher he will probably sooner or later find a need to meet in some fashion with his colleagues for the mutual exchange of ideas and inspiration. This gathering together by researchers has, as you well know, been formalized in scientific societies.

Now there are two kinds of scientific societies of which we, as pharmacologists, can become affiliated. The first groups I will dismiss briefly because these are easy to join and, of course, I would urge you to join them for through them you can give and receive benefit. There is the American Pharmaceutical Association. You can join this by having a friend sign your application blank and sending in a check for initiation fee and dues. There is the American Association for the Advancement of Science which operates very much the same way and your affiliation is really the result of your interest in belonging. The two societies which fall into a different category with respect to our field are the American Society for Pharmacology and Experimental Therapeutics and the Society for Experimental Biology and Medicine and I want to talk about these separately; but first, neither can be joined, in the simple sense of the word. Both of these societies have standards for admission to membership.

I know most about the American Society for Pharmacology and Experimental Therapeutics because for four years I have been treasurer and council member. First I would like to dispel some misinformation about this Society. This is the belief that there is discrimination against pharmacologists in schools of pharmacy. There is no foundation to this. A person is elected to membership in this Society by the present members after recommendation and submission of supporting evidence by two members. Now this means that theoretically the individual does not know that he is being proposed for membership. Practically speaking, an individual who thinks that he has done creditable research and would like to affiliate with the Society may privately ask one of his friends who is a member if he will recommend him. This member who is sincere in wanting new strong members will look into the qualifications of this candidate. The qualifications are really very simple. They are mainly two. First, the publication of creditable scientific papers in pharmacology. And second, the likelihood that the individual will continue to be a pharmacologist. The recommendation with a co-signer is received by the membership committee, the council and finally voted on by the members. Thus membership is a valued honor that represents the approbation of one's colleagues. In a manner of speaking, election of membership in the Pharmacology Society is a little like approval by a specialty board in medicine. On the basis of what I have just said you can see that I or any

member would be glad to propose anyone who could possibly qualify for membership in the Society. Now, unhappily, some individuals have such flimsy bibliographies or have such weak evidence of independent research that it's too much of a hazard for a member to propose them. And I would say that in the members of the Society, generally, a proposal for membership is taken very seriously and recommendations are not made lightly.

The second society I would like to describe is The Society for Experimental Biology and Medicine. This is also a society to which one is nominated and elected to membership. It is a little more difficult to become a member here because of the organization of the Society on a sectional basis. If you are in a city--Chicago, for example--where there is a very active section and you are doing pharmacology or indeed experimental biology of any kind, it is almost inevitable that some member of the Chicago Society would invite you to give a paper at one of their local section meetings. In due time you would be nominated and elected to membership. If one is located in a geographic area where there is no section, one must contact some member in a nearby geographic region and ask him if he would be willing to nominate you. In other words, Sections have the privilege of electing members in areas where there is no Section of the Society.

Next I would like to tell you a development that is taking place on the West Coast because many of you are from this area. This is the development of a Western Pharmacology Society. This has grown out of the attendance by maybe a dozen pharmacologists of the Western Society for Clinical Research meetings which take place in January every year in Carmel. The present plan is to have a meeting this January just preceding the meetings of the Western Clinical Society. A program is being planned and undoubtedly there will be a formal plan of organization for future meetings observed. I hope those of you who can will follow and support this new development in pharmacology.

SUMMARY OF THE TEACHERS' SEMINAR ON PHARMACOLOGY

Tom D. Rowe, Ewart A. Swinyard, and Theodore Brody

Presented by Dean Rowe

Because the 1951 Seminar on Pharmacology dealt primarily with teaching methods and the 1954 Teachers' Seminar dealt entirely with pedagogical procedures, the Committee decided this year's program should emphasize what to teach in selected areas of pharmacology. This concept is in agreement with the original purposes of the Seminars as outlined in the Findings and Recommendations of the Pharmaceutical Survey as follows: "The primary purpose of these Seminars is that of providing needed opportunity for the members of the teaching staff and for graduate students to come into fruitful contact and to keep pace with progressive content and methods of pharmaceutical teaching."

To carry out the objectives of presenting course material the Committee selected a highly competent faculty composed of men particularly well known for their knowledge of and research in various phases of pharmacology. In order to get the best known specialists in certain areas it was necessary to draw heavily on men not associated with pharmacy schools but who were connected with medical schools or industry. Because of this selection the Seminar was different from previous ones in other disciplines where it was not possible to call on specialists from other fields to such a great extent. The arrangement was especially well adapted to the field of pharmacology because as Dean Daniels stated in his paper, "Pharmacology is the common meeting ground of pharmacy and medicine."

During the first day the background was laid for the discussion of developments in pharmacology. Among the many points discussed perhaps the following were the most important:

1. There is definite need for strengthening the biological sequence in colleges of pharmacy. Dr. Green compared the situation today with that reported by Deno in 1951 and called attention to the progress which has been made. Perhaps the most impressive improvement was in the teaching of some form of anatomy: a total of forty schools now teach anatomy either separately or as part of an integrated course with physiology, whereas only 13 gave some instruction in this area in 1951. Even with this progress much remains to be accomplished. For example, not all schools require work in either biology or zoology.

It was emphasized that a proper biological sequence is necessary in order to provide a good background for a strong course in physiology which in turn is absolutely essential for a sound course in pharmacology.

There is some disagreement as to the specific courses to be offered in the sequence, such as gross anatomy versus some form of comparative anatomy. Nevertheless, there is general agreement that some type of anatomy, as well as strong courses in physiology and biochemistry are necessary if pharmacology is to be

taught on a proper level. Biochemistry and physiology courses equivalent to those offered in medical schools appear to be essential to meet this requirement. This point was stressed throughout the Seminar by direct statements. The importance of the biochemical approach to pharmacology was further emphasized indirectly by the presentation of methods of research now being done in this area.

2. Every paper presented during the first day mentioned the need for better grounding in terminology. While no one answer was given for this problem, it was obvious that pharmacy students were not sufficiently familiar with medical terminology. More study of this problem by all pharmacy teachers regardless of their specialty is urgently needed.

3. Pharmacology is one of the most important courses in the pharmacy curriculum. To the pharmacologist it is, of course, the most important. Allowing for this understandably biased viewpoint it was adequately demonstrated that knowledge of pharmacology is essential to the successful operation of a retail store, to the hospital pharmacist, to the detail man, and to all other branches of pharmacy.

Industrial applications of pharmacology are constantly expanding and many companies other than pharmaceutical manufacturers are requiring the services of professional pharmacologists. In some of these, the pharmacologists are not concerned with the effect of drugs but with the effect of intermediates and products encountered by the factory workers in their daily tasks. Because of this broader base of operations, more and more pharmacologists with graduate training are needed.

4. In looking toward the future it appears that pharmacology will become increasingly important to the pharmacist. Pharmacy training in the future, including pharmacology, will enable the pharmacist to take a more important and active part in the activities of the health team.

During the week it became obvious that the usual experimental pharmacological approach to the solution in this field was just one of several procedures now in common use. The most important of the others are the biochemical and the clinical approaches.

Although the biochemical techniques applied to pharmacology are comparatively new, it is already evident that such methods are beginning to occupy a position of importance in the study of pharmacology. Teachers of pharmacology in our schools of pharmacy, if not so already, should be keenly aware of and keep abreast of the developments in this area. This field presents excellent possibilities for research in pharmacy schools.

The unique methods for studying cardiac drugs and cardiac function while obviously beyond the resources of most pharmacy schools demonstrate the value of ingenuity and illustrate what can be accomplished by an imaginative mind. The presentation of these complicated and expensive procedures should not discourage those teachers whose facilities and funds are limited. On the contrary, they might serve to stimulate them to develop original problems possible within the limits of their available resources.

While the motion pictures shown would have little direct teaching value in a beginning course in pharmacology, they would have tremendous impact by showing the pharmacy student the complexity of pharmacological research and what is done in some cases before a new drug reaches clinical acceptance. For this reason it would be helpful if it were possible for the films shown by Dr. West, Dr. Rushmer, and Dr. Kroeger to be made generally available to teachers presenting pharmacology to our students.

While these unique experiments are valuable for the elucidation of basic mechanisms of drug action and the use of drugs as tools for the study of the physiological and biochemical substrata on which drug actions are based, they do not replace basic laboratory procedures for the evaluation of potentially useful therapeutic agents.

Many obstacles are encountered which limit the predictive value of currently employed laboratory screening procedures. Nevertheless, the definitive study of drugs and drug mechanisms is a process which must continue long after the drug has been introduced as a therapeutic agent.

Important facets of drug evaluation are proper experimental design and judicious treatment of data; one cannot make a bad experiment into a good one by using statistics. Statistics are valuable only if used and interpreted properly. While statistics are important in certain types of experiments, pharmacy teachers should realize that much pharmacological research can be accomplished without such treatment.

Ultimately, the test of whether or not a drug is of value in the practice of medicine is its effect on man. The importance of good clinical evaluation programs is self-evident. While research in this area is limited to physicians or to pharmacologists working in close cooperation with physicians, data obtained from clinical studies should be utilized in presenting pharmacology to pharmacy students. Pharmacy students should be made aware of the general methods used in the clinical evaluation of drugs such as the double-blind technique, cross-over methods of testing, and use of placebos. Limitations of these methods should also be recognized. The importance of the role of the psyche in human experiments should be emphasized to the students.

A good example of the role of the psyche is apparent in the attempts to evaluate clinically the mood-altering drugs. Teachers should be extremely cautious in presenting positive conclusions concerning these drugs derived from either clinical or experimental observation. They should follow carefully the current intensive research in this field.

Graduate Training in Pharmacology

The papers presented on this subject re-emphasized the many requirements to be met for a satisfactory graduate program. Among these are adequate staff and availability of numerous specialized ancillary courses. These needs are apt to be overlooked or minimized in pharmacy schools when inaugurating graduate programs. If I may be permitted a personal observation, I believe this is a serious

mistake and one which should be given primary consideration in starting a graduate program. Pharmacology graduate training at the Ph.D. level requires more than two staff members, and more than one or two advanced courses in pharmacology with some research added to produce a competent pharmacologist.

While the expense involved in offering graduate work in pharmacology was not mentioned directly, it was mentioned indirectly by the listing of requirements. Perhaps no area in pharmacy costs more to operate on a graduate level than does pharmacology. Schools not in a position to meet these expenses should not undertake graduate work either on the M.S. or Ph.D. level. This does not mean that no research should be done. It can and should be done to the limit of the resources available. Graduate work, however, cannot be done properly on a shoestring basis.

Graduate seminars and teaching by graduate students are important aspects in the training program.

Dr. Dille's points concerning membership and participation in professional societies are especially timely. It is unfortunate that more pharmacology teachers in pharmacy schools are not members of the American Society for Pharmacology and Experimental Therapeutics. It seems to me as important for teachers to be members of their specialized groups as it is for them to belong to the American Pharmaceutical Association. I am confident that many of our group are eligible for membership in the Society, and I hope they will take advantage of their eligibility. We cannot expect to be accorded the recognition we seek until we are on equal footing with our colleagues in other branches of pharmacology. The Society has much to offer our teachers at their semi-annual meetings and especially at the annual fall Teachers' Symposium on Pharmacology. This year's Symposium will be held in Baltimore, September 3-7. I have been informed that all pharmacy teachers are invited to attend whether or not they are members of the Society. In 1958 the Symposium will be held in Ann Arbor the last week in August. You are cordially invited to come.

It is difficult to assess today the specific values of the sessions we have attended the past week. The nature of the program with its emphasis on research makes immediate conclusions difficult to draw. I believe the full value of the presentations will come when we have had time to reflect on them, to study the papers when they become available in the Proceedings, and to utilize the information from time to time during the coming year. This has not been a package deal where everything has been neatly wrapped and properly labeled. Instead it has been a thought-provoking meeting presented on a high level with many hidden values present. In the long-run I believe we may conclude that it will prove to be of extreme value to the pharmacology teachers in our colleges of pharmacy.

On behalf of the American Association of Colleges of Pharmacy, I wish to thank Dean Orr and his committee for the splendid program which they arranged. Our sincere thanks also to the faculty members for their fine contributions. I know we all have enjoyed being in Seattle and the University of Washington this week. Besides arranging a good meeting, Dean Orr and his colleagues at the College of Pharmacy made our stay pleasant in every way. We deeply appreciate the many courtesies and the gracious hospitality extended to us. We leave Seattle and its beauty and air-conditioned climate reluctantly, but with fond memories and the hope that we can return again soon.

PHARMACOLOGY SEMINAR ROSTER
July 14-19, 1957

Adams, John G., Duquesne University, Pittsburgh, Pennsylvania
Althouse, Harry, Sandoz Pharmaceuticals, San Francisco, California
Anderson, Edmund G., University of Washington, Seattle, Washington
Anderson, L. J., Washington State College, Pullman, Washington
Andries, Maurice C., Drake University, DesMoines, Iowa
Appelo, Mrs. Burton, Deep River, Washington
Bang, Haakon, Washington State College, Pullman, Washington
Barnes, Byron A., St. Louis College of Pharmacy, St. Louis, Missouri
Beecher, Henry K., Harvard Medical School, Boston, Massachusetts
Bester, John F., University of Southern California, Los Angeles, California
Bilden, Howard M., Ciba Pharmaceutical Products, Inc., Westfield, New Jersey
Brodie, Donald C., University of California, San Francisco, California
Brody, Theodore M., University of Michigan, Ann Arbor, Michigan
Buckley, Joseph P., University of Pittsburgh, Pittsburgh, Pennsylvania
Coker, Samuel T., University of Kansas City, Kansas City, Kansas
Daniels, Troy C., University of California, San Francisco, California
Davis, John E., University of Texas, Austin, Texas
Davis, W. Marvin, University of Oklahoma, Norman, Oklahoma
Dille, James M., University of Washington, Seattle, Washington
Drill, Victor, G. D. Searle & Co., Chicago, Illinois
Dorpat, Theodore L., University of Washington, Seattle, Washington
Dunham, Norris W., Ferris Institute, Big Rapids, Michigan
Elder, John T., Jr., University of Washington, Seattle, Washington
Fagg, B. Grant, Kirkman Pharmacal Co., Seattle, Washington
Falk, Gertrude, University of Washington, Seattle, Washington
Fingl, Edward, University of Utah, Salt Lake City, Utah
Fischer, Louis, University of Washington, Seattle, Washington
Forslund, Herman C., Oregon State College, Corvallis, Oregon
Fox, Lauretta E., University of Florida, Gainesville, Florida
Frederickson, Evan, University of Washington, Seattle, Washington
Gale, Laurence E., Idaho State College, Pocatello, Idaho
Galysh, Fred T., North Dakota Agriculture College, Fargo, North Dakota
Gault, Alta R., University of Mississippi, Oxford, Mississippi
Gautieri, Ronald, Temple University, Philadelphia, Pennsylvania
Gibson, Melvin R., Washington State College, Pullman, Washington
Gibson, Robert D., University of Nebraska, Lincoln, Nebraska
Goodrich, Forest J., University of Washington, Seattle, Washington
Green, Donald E., Washington State College, Pullman, Washington
Green, Melvin W., American Council on Pharmaceutical Education, Chicago, Illinois
Gogerty, John H., University of Washington, Seattle, Washington
Haley, Thomas J., UCLA Atomic Energy Project, Los Angeles, California
Hall, Nathan A., University of Washington, Seattle, Washington
Halliday, John E., University of British Columbia, Vancouver, British Columbia
Hammond, Phillip V., Howard University, Washington, D. C.
Hazleton, Lloyd W., Hazleton Laboratories, Falls Church, Virginia

Holland, William C., Vanderbilt Medical School, Nashville, Tennessee
Horita, Akira, University of Washington, Seattle, Washington
Huitric, Alain C., University of Washington, Seattle, Washington
Hunt, Edgar Lee, University of Southern California, Los Angeles, California
Ichniowski, C. T., University of Maryland, Baltimore, Maryland
Ireland, Edward J., Loyola University of the South, New Orleans, Louisiana
Jenkins, Howard, Massachusetts College of Pharmacy, Boston, Massachusetts
Johnson, Douglas, Southern College of Pharmacy, Decatur, Georgia
Johnson, William E., University of Wyoming, Laramie, Wyoming
Jordin, M. W., University of Arkansas, Little Rock, Arkansas
Kahl, Raymond J., University of Wyoming, Laramie, Wyoming
Keasling, Hugh H., State University of Iowa, Iowa City, Iowa
Kincaid, F. Dale, Parke, Davis & Co., Seattle, Washington
Kopet, Jerome C., Spokane, Washington
Kroeger, D. C., University of Texas, Houston, Texas
Krupski, Edward, University of Washington, Seattle, Washington
Kudalkar, Vasant G., University of Washington, Seattle, Washington
Leake, C. D., Ohio State University, Columbus, Ohio
Leonard, R. M., George Washington University, Washington, D. C.
Levy, Joe, University of Washington, Seattle, Washington
Lindsay, Dale R., Nat'l. Institutes of Health, Bethesda, Maryland
Lingenfelter, John, Seattle, Washington
Logan, G. A., University of Washington, Seattle, Washington
Magee, Donald F., University of Washington, Seattle, Washington
Matthews, R. A., University of British Columbia, Vancouver, British Columbia
McCarthy, Walter C., University of Washington, Seattle, Washington
McCutcheon, R. S., Oregon State College, Corvallis, Oregon
Meyers, Frederick H., University of California, San Francisco, California
Miller, Chester I., State University of Iowa, Iowa City, Iowa
Mittelstaedt, Stanley, University of Arkansas, Little Rock, Arkansas
Morris, Ralph, University of Illinois, Chicago, Illinois
Morrison, Robert W., University of South Carolina, Columbia, South Carolina
Mulvey, Richard K., Wayne State University, Detroit, Michigan
Murray, J. R., University of Alberta, Edmonton, Alberta, Canada
Nash, Charles W., University of Alberta, Edmonton, Alberta, Canada
Orr, J. E., University of Washington, Seattle, Washington
Pettinato, Frank A., University of Washington, Seattle, Washington
Phatak, N. W., University of Oregon Dental School, Portland, Oregon
Picchioni, Albert L., University of Arizona, Tucson, Arizona
Platcow, Edward L., Ferris Institute, Big Rapids, Michigan
Plein, Elmer M., University of Washington, Seattle, Washington
Plein, Joy B., University of Washington, Seattle, Washington
Rau, Billy, Howard College, Birmingham, Alabama
Redman, Kenneth, South Dakota State College, Brookings, South Dakota
Rising, L. Wait, University of Washington, Seattle, Washington
Rodman, Morton J., Rutgers University, Newark, New Jersey
Roscoe, Charles W., University of Washington, Seattle, Washington
Rossi, G. Victor, Philadelphia Coll. of Pharm. & Sci., Philadelphia, Pennsylvania
Rowe, Tom D., University of Michigan, Ann Arbor, Michigan
Rushmer, Robert F., University of Washington, Seattle, Washington
Russell, Robert L., University of Missouri, Columbia, Missouri

Saxe, L. H., West Virginia University, Morgantown, West Virginia
Scott, Paul M., Washington State College, Pullman, Washington
Sim, S. K., University of British Columbia, Vancouver, British Columbia
Smith, E. Byrcn, Pacific Drug Review, Portland, Oregon
Sullivan, Jeremiah B., Jr., University of Washington, Seattle, Washington
Swinyard, Ewart A., University of Utah, Salt Lake City, Utah
Tozer, George, Everett Junior College, Everett, Washington
Voigt, Ralph F., University of Illinois, Chicago, Illinois
Way, E. Leong, University of California, San Francisco, California
Webber, T. C., Schering Corporation, Seattle, Washington
Webster, George L., University of Illinois, Chicago, Illinois
Wenzel, Duane G., University of Kansas, Lawrence, Kansas
West, Theodore C., University of Washington, Seattle, Washington
Westfall, B. A., University of Missouri, Columbia, Missouri
Wheelun, Homer, Seattle, Washington
White, Wallace F., University of Minnesota, St. Paul, Minnesota
Wood, James A., University of Saskatoon, Saskatoon, Saskatchewan, Canada
Zopf, Louis C., State University of Iowa, Iowa City, Iowa

PROGRAM

TEACHERS' SEMINAR ON PHARMACOLOGY

Sunday, July 14

1:00-7:00 p.m.	Registration Lobby, Men's Residence Hall
6:30 p.m.	Buffet Supper Dining Room, Men's Residence Hall
8:00 p.m.	Opening Session Jack E. Orr, Presiding Dining Room, Men's Residence Hall
	Address of Welcome - Dr. Henry Schmitz, President, University of Washington
	Greetings from the American Foundation for Pharmaceutical Education - Dr. W. Paul Briggs, Secretary and Executive Director
	Greetings from the American Association of Colleges of Pharmacy - Dean Tom D. Rowe, President
	Address - Dr. Chauncey D. Leake, Assistant Dean, College of Medicine, Ohio State University

LADIES' PROGRAM

Sunday, July 14	Buffet Supper and Opening Exercises
Monday, July 15	Luncheon - Hostesses, College of Pharmacy Faculty Wives
Tuesday, July 16	Sightseeing Tours Tea at the home of Dean and Mrs. Jack E. Orr
Wednesday, July 17	Fashion Luncheon (no-host), Frederick & Nelson Tearoom Penthouse Theatre Party (no-host)
Thursday, July 18	Salmon Bake - Seward Park

INVENTORY AND PROSPECTUS
E. A. Swinyard, Chairman

Monday, July 15

8:00-9:00	Registration
9:00	Opening Remarks
9:05	The Status and Needs of Pharmacology in the Pharmaceutical Curriculum - Melvin W. Green
9:30	Discussion
9:45	The Use of Pharmacology in Retail Pharmacy - J. C. Kopet
10:05	Discussion
10:15	Coffee
10:35	The Use of Pharmacology in Hospital Pharmacy - Louis C. Zopf
10:55	Discussion
11:05	The Use of Pharmacology in Industry - Victor A. Drill
11:25	Discussion
11:35	The Use of Pharmacology in Detailing - Howard M. Bilden
11:55	Discussion
12:30	Lunch
2:00	Optimum Prerequisites to the Undergraduate Course in Pharmacology - Troy C. Daniels
2:30	Discussion
2:45	Pharmacology in the Pharmaceutical Curriculum of the Future - John G. Adams
3:15	Discussion
3:30	Coffee
3:45	Discussion and Summary

MECHANISMS AND METHODS IN PHARMACOLOGY
T. C. Daniels, Chairman

Tuesday, July 16

9:00	Opening Remarks
9:05	Biochemical Approach to Pharmacology - William C. Holland
9:35	Discussion
9:45	Laboratory Evaluation of Drugs - Ewart A. Swinyard
10:15	Discussion
10:25	Coffee
10:40	Clinical Evaluation of Drugs - Henry K. Beecher
11:10	Discussion
11:20	Experimental Design - Edward Fingl
11:50	Discussion
12:30	Lunch Group Discussion on Problems of Drug Mechanisms, Drug Evaluation, and Experimental Design - Drs. Beecher, Holland, Fingl, and Swinyard
2:00	Session I
3:00	Coffee
3:15	Session II

INTERPRETATION OF DRUG EFFECTS ON THE HEART
T. C. West, Chairman

Wednesday, July 17

9:00	Opening Remarks
9:05	Basic Concepts of Cardiac Pharmacology - William C. Holland
9:25	Discussion
9:35	Laboratory Approaches: Unicellular Recording - Theodore C. West
10:05	Discussion
10:15	Coffee
10:30	Laboratory Approaches: Ventricular Performance and Its Measurement - Robert F. Rushmer
11:10	Discussion
11:20	Laboratory Approaches: Effects of Cardiac Drugs on Biochemical Processes - William C. Holland
12:00	Discussion
12:30	Lunch
2:00	Clinical Approaches - Gordon A. Logan
2:45	Discussion
2:55	Round Table Discussion: Importance of Animal Experiments to the Clinical Use of Cardiac Drugs - Drs. Holland, Logan, Rushmer and West
3:45	Coffee
4:00	Demonstrations: Microelectrode Recording from Heart Muscle Recording Ventricular Function in the Dog Recording Cardiac Function in the Human

CURRENT CONCEPTS IN PSYCHOPHARMACOLOGY
J. M. Dille, Chairman

Thursday, July 18

9:00	Introduction
9:30	A Survey of the Mood Altering Drugs - Chauncey D. Leake
10:15	Discussion
10:30	Coffee
10:50	Biochemical Approach to Mental Illness - Akira Horita
11:40	Discussion
12:30	Lunch
2:00	The Pharmacological Approach to Mental Illness - Thomas J. Haley
2:45	Discussion
3:00	Coffee
3:15	Clinical Problems and the Psychopharmacological Agents - Theodore L. Dorpat
3:45	Discussion and Summary
6:00	Salmon Bake, Seward Park

GRADUATE TRAINING AND RESEARCH IN PHARMACOLOGY

G. L. Webster, Chairman

Friday, July 19

9:00	Opening Remarks
9:05	Objectives of Graduate Training in Pharmacology - Victor A. Drill
9:35	Discussion
9:45	Prerequisites for the Pharmacology Graduate Student - E. Leong Way
10:15	Discussion
10:25	Coffee
10:40	Supplemental Training at the Graduate Level - Ewart A. Swinyard
11:10	Discussion
11:20	The Development of a Pharmacology Research Program - John E. Davis
11:50	Discussion
12:30	Lunch
2:00	Financial Support for Research - Dale R. Lindsay
2:25	Discussion
2:50	The Importance of Professional Affiliation to a Graduate Program in Pharmacology - James M. Dille
3:10	Discussion
3:20	Concluding Remarks - Tom D. Rowe Adjournment